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(54) **ANTI-TCR ANTIBODY MOLECULES AND USES THEREOF**

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See application file for complete search history.

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(57) **ABSTRACT**

The disclosure provides antibody molecules that bind to TCR Vβ regions and multispecific molecules comprising said antibody molecules. Additionally, disclosed are nucleic acids encoding the same, methods of producing the aforesaid molecules, pharmaceutical compositions comprising aforesaid molecules, and methods of treating a cancer using the aforesaid molecules.

29 Claims, 97 Drawing Sheets

Specification includes a Sequence Listing.

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* cited by examiner

VH

Framework 1 | CDR 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
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SEQ ID NO: 9	Q	V	Q	L	V	Q	S	G	A	E	V	K	K	P	G	S	S	V	K	V	S	C	K	A	S	G	Y	S	F	T	T	Y	I	H

Framework 2 | CDR 2

	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	52a	53	54	55	56	57	58	59	60	61	62	63	64	65
SEQ ID NO: 1	W	V	K	Q	R	P	G	Q	G	L	E	W	I	G	W	F	P	G	S	G	N	I	K	Y	N	E	K	F	K	G
SEQ ID NO: 9	W	V	R	Q	A	P	G	Q	G	L	E	W	M	G	W	F	P	G	S	G	N	I	K	Y	N	E	K	F	K	G

	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	82a	82b	82c	83	84	85	86	87	88	89	90	91	92	93	94
SEQ ID NO: 1	K	A	T	L	T	A	D	T	S	S	S	T	A	Y	M	Q	L	S	S	L	T	S	E	E	S	A	V	Y	Y	F	C	A	G
SEQ ID NO: 9	R	V	T	I	T	A	D	T	S	T	S	T	A	Y	M	E	L	S	S	L	R	S	E	D	T	A	V	Y	Y	C	A	G

CDR 3 | Framework 4

	95	96	97	98	99	100	100a	100b	101	102	103	104	105	106	107	108	109	110	111	112	113
SEQ ID NO: 1	S	Y	Y	S	Y	D	V	L	D	Y	W	G	H	G	T	T	L	T	V	S	S
SEQ ID NO: 9	S	Y	Y	S	Y	D	V	L	D	Y	W	G	Q	G	T	T	V	T	V	S	S

FIG. 1A

VL

Framework 1 / CDR 1

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
SEQ ID NO: 2	D	I	L	M	T	Q	S	Q	K	F	M	S	T	S	L	G	D	R	V	S	V	S	C	*K*	*A*	*S*	*Q*	*N*	*V*	*G*	*I*	*N*	*V*	*V*
SEQ ID NO: 10	D	I	Q	M	T	Q	S	P	S	F	L	S	A	S	V	G	D	R	V	T	I	T	C	*K*	*A*	*S*	*Q*	*N*	*V*	*G*	*I*	*N*	*V*	*V*
SEQ ID NO: 11	D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	*K*	*A*	*S*	*Q*	*N*	*V*	*G*	*I*	*N*	*V*	*V*

Framework 2 / CDR 2

	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56
SEQ ID NO: 2	W	H	Q	Q	K	P	G	Q	S	P	K	A	L	I	Y	*S*	*S*	*S*	*H*	*R*	*Y*	*S*
SEQ ID NO: 10	W	H	Q	Q	K	P	G	K	A	P	K	A	L	I	Y	*S*	*S*	*S*	*H*	*R*	*Y*	*S*
SEQ ID NO: 11	W	H	Q	Q	K	P	G	K	V	P	K	A	L	I	Y	*S*	*S*	*S*	*H*	*R*	*Y*	*S*

Framework 3

	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88
SEQ ID NO: 2	G	V	P	D	R	F	T	G	S	G	S	G	T	D	F	T	L	T	I	N	N	V	Q	S	E	D	L	A	E	Y	F	C
SEQ ID NO: 10	G	V	P	S	R	F	S	G	S	G	S	G	T	E	F	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	F	C
SEQ ID NO: 11	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I	S	S	L	Q	P	E	D	V	A	T	Y	F	C

CDR 3 / Framework 4

	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107
SEQ ID NO: 2	*Q*	*Q*	*F*	*K*	*S*	*Y*	*P*	*L*	*T*	F	G	A	G	T	K	L	E	L	K
SEQ ID NO: 10	*Q*	*Q*	*F*	*K*	*S*	*Y*	*P*	*L*	*T*	F	G	Q	G	T	K	L	E	I	K
SEQ ID NO: 11	*Q*	*Q*	*F*	*K*	*S*	*Y*	*P*	*L*	*T*	F	G	Q	G	T	K	L	E	I	K

FIG. 1B

VH

	Framework 1																									CDR 1									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
SEQ ID NO: 15	D	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	R	K	L	S	C	A	A	S	G	F	T	F	S	N	F	G	M	H
SEQ ID NO: 23	Q	V	Q	L	V	E	S	G	G	G	V	V	Q	P	G	R	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	F	G	M	H
SEQ ID NO: 24	E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	F	G	M	H
SEQ ID NO: 25	E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	L	S	C	A	A	S	G	F	T	F	S	N	F	G	M	H

	Framework 2																									CDR 2									
	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	52a	53	54	55	56	57	58	59	60	61	62	63	64	65				
SEQ ID NO: 15	W	V	R	Q	A	P	D	K	G	L	E	W	V	A	Y	I	S	S	G	S	S	T	I	Y	Y	A	D	T	L	K	G			
SEQ ID NO: 23	W	V	R	Q	A	P	G	K	G	L	E	W	V	A	Y	I	S	S	G	S	S	T	I	Y	Y	A	D	T	L	K	G			
SEQ ID NO: 24	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	Y	I	S	S	G	S	S	T	I	Y	Y	A	D	T	L	K	G			
SEQ ID NO: 25	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	Y	I	S	S	G	S	S	T	I	Y	Y	A	D	T	L	K	G			

	Framework 3																																		
	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	82a	82b	82c	83	84	85	86	87	88	89	90	91	92	93	94			
SEQ ID NO: 15	R	F	T	I	S	R	D	N	P	K	N	T	L	F	L	Q	M	T	S	L	R	S	E	D	T	A	M	Y	Y	C	A	R		
SEQ ID NO: 23	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R		
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SEQ ID NO: 25	R	F	T	I	S	R	D	N	S	K	N	T	L	Y	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R		

	CDR 3																									Framework 4									
	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113																
SEQ ID NO: 15	R	G	E	G	A	M	D	Y	W	G	Q	G	T	S	V	T	V	S	S																
SEQ ID NO: 23	R	G	E	G	A	M	D	Y	W	G	Q	G	T	T	V	T	V	S	S																
SEQ ID NO: 24	R	G	E	G	A	M	D	Y	W	G	Q	G	T	T	V	T	V	S	S																
SEQ ID NO: 25	R	G	E	G	A	M	D	Y	W	G	Q	G	T	T	V	T	V	S	S																

FIG. 2A

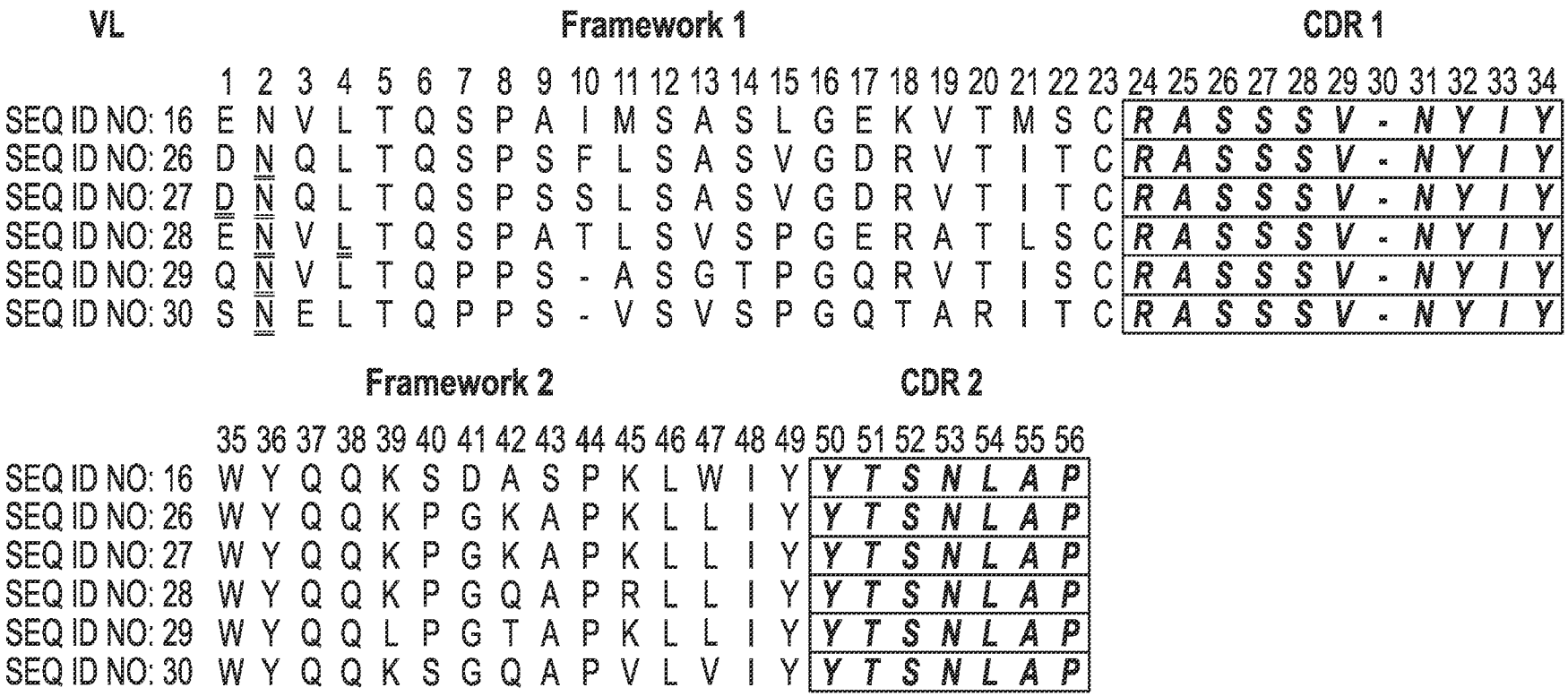

VL
Framework 1
CDR 1
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
SEQ ID NO: 16 E N V L T Q S P A I M S A S L G E K V T M S C R A S S S V - N Y I Y
SEQ ID NO: 26 D N Q L T Q S P S F L S A S V G D R V T I T C R A S S S V - N Y I Y
SEQ ID NO: 27 D N Q L T Q S P S S L S A S V G D R V T I T C R A S S S V - N Y I Y
SEQ ID NO: 28 E N V L T Q S P A T L S V S P G E R A T L S C R A S S S V - N Y I Y
SEQ ID NO: 29 Q N V L T Q P P S - A S G T P G Q R V T I S C R A S S S V - N Y I Y
SEQ ID NO: 30 S N E L T Q P P S - V S V S P G Q T A R I T C R A S S S V - N Y I Y
Framework 2
CDR 2
35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56
SEQ ID NO: 16 W Y Q Q K S D A S P K L W I Y Y T S N L A P
SEQ ID NO: 26 W Y Q Q K P G K A P K L L I Y Y T S N L A P
SEQ ID NO: 27 W Y Q Q K P G K A P K L L I Y Y T S N L A P
SEQ ID NO: 28 W Y Q Q K P G Q A P R L L I Y Y T S N L A P
SEQ ID NO: 29 W Y Q Q L P G T A P K L L I Y Y T S N L A P
SEQ ID NO: 30 W Y Q Q K S G Q A P V L V I Y Y T S N L A P

FIG. 2B

Framework 3

	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88
SEQ ID NO: 16	G	V	P	T	R	F	S	G	S	G	S	G	N	S	Y	S	L	T	I	S	S	M	E	G	E	D	A	A	T	Y	Y	C
SEQ ID NO: 26	G	V	P	S	R	F	S	G	S	G	S	G	N	E	Y	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C
SEQ ID NO: 27	G	V	P	S	R	F	S	G	S	G	S	G	N	D	Y	T	L	T	I	S	S	L	Q	P	E	D	F	A	T	Y	Y	C
SEQ ID NO: 28	G	I	P	A	R	F	S	G	S	G	S	G	N	E	Y	T	L	T	I	S	S	L	Q	S	E	D	F	A	V	Y	Y	C
SEQ ID NO: 29	G	V	P	D	R	F	S	G	S	G	S	G	N	S	Y	S	L	A	I	S	G	L	R	S	E	D	E	A	D	Y	Y	C
SEQ ID NO: 30	G	I	P	E	R	F	S	G	S	G	S	G	N	M	Y	T	L	T	I	S	G	A	Q	V	E	D	E	A	D	Y	Y	C

CDR 3 Framework 4

	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107
SEQ ID NO: 16	Q	Q	F	T	S	S	P	F	T	F	G	S	G	T	K	L	E	I	K
SEQ ID NO: 26	Q	Q	F	T	S	S	P	F	T	F	G	Q	G	T	K	L	E	I	K
SEQ ID NO: 27	Q	Q	F	T	S	S	P	F	T	F	G	Q	G	T	K	L	E	I	K
SEQ ID NO: 28	Q	Q	F	T	S	S	P	F	T	F	G	Q	G	T	K	L	E	I	K
SEQ ID NO: 29	Q	Q	F	T	S	S	P	F	T	F	G	T	G	T	K	V	T	V	L
SEQ ID NO: 30	Q	Q	F	T	S	S	P	F	T	F	G	T	G	T	K	V	T	V	L

FIG. 2B
(Continued)

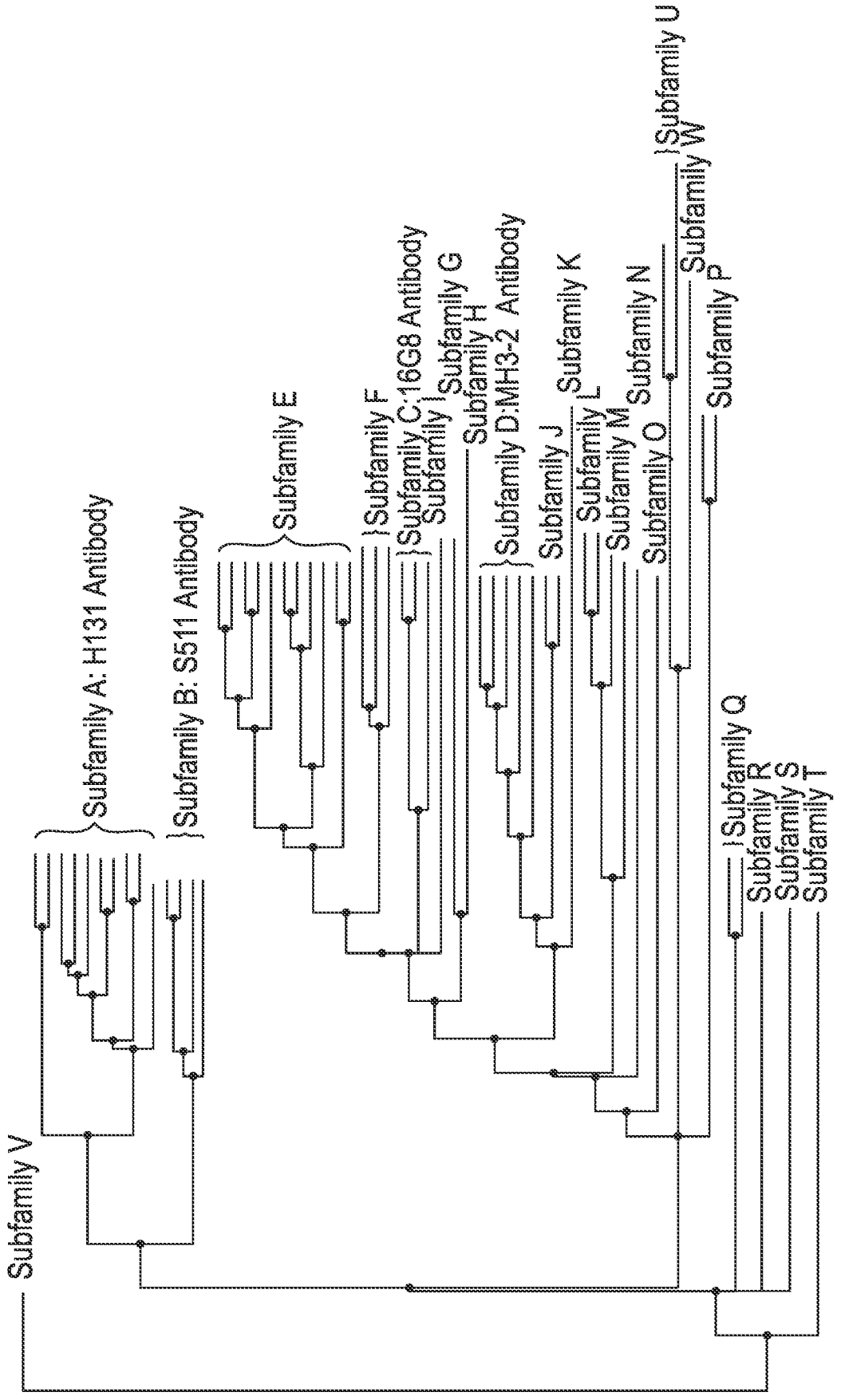

Subfamily V
Subfamily A: H131 Antibody
Subfamily B: S511 Antibody
Subfamily E
Subfamily F
Subfamily C:16G8 Antibody
Subfamily I
Subfamily G
Subfamily H
Subfamily D:MH3-2 Antibody
Subfamily J
Subfamily K
Subfamily L
Subfamily M
Subfamily N
Subfamily O
Subfamily U
Subfamily W
Subfamily P
Subfamily Q
Subfamily R
Subfamily S
Subfamily T

FIG. 3

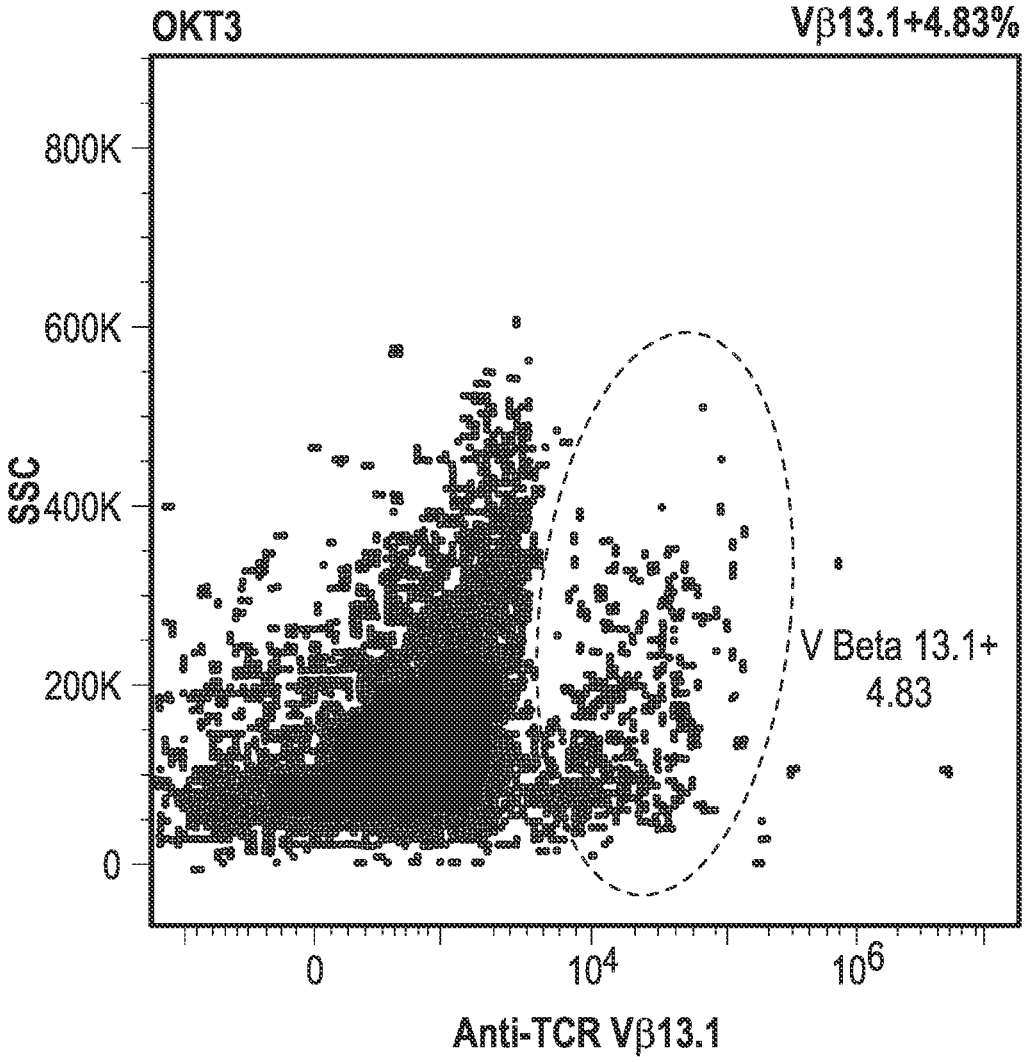

OKT3
Vβ13.1+4.83%
800K
600K
400K
200K
0
SSC
V Beta 13.1+
4.83
0
10^4
10^6
Anti-TCR Vβ13.1

FIG. 4A

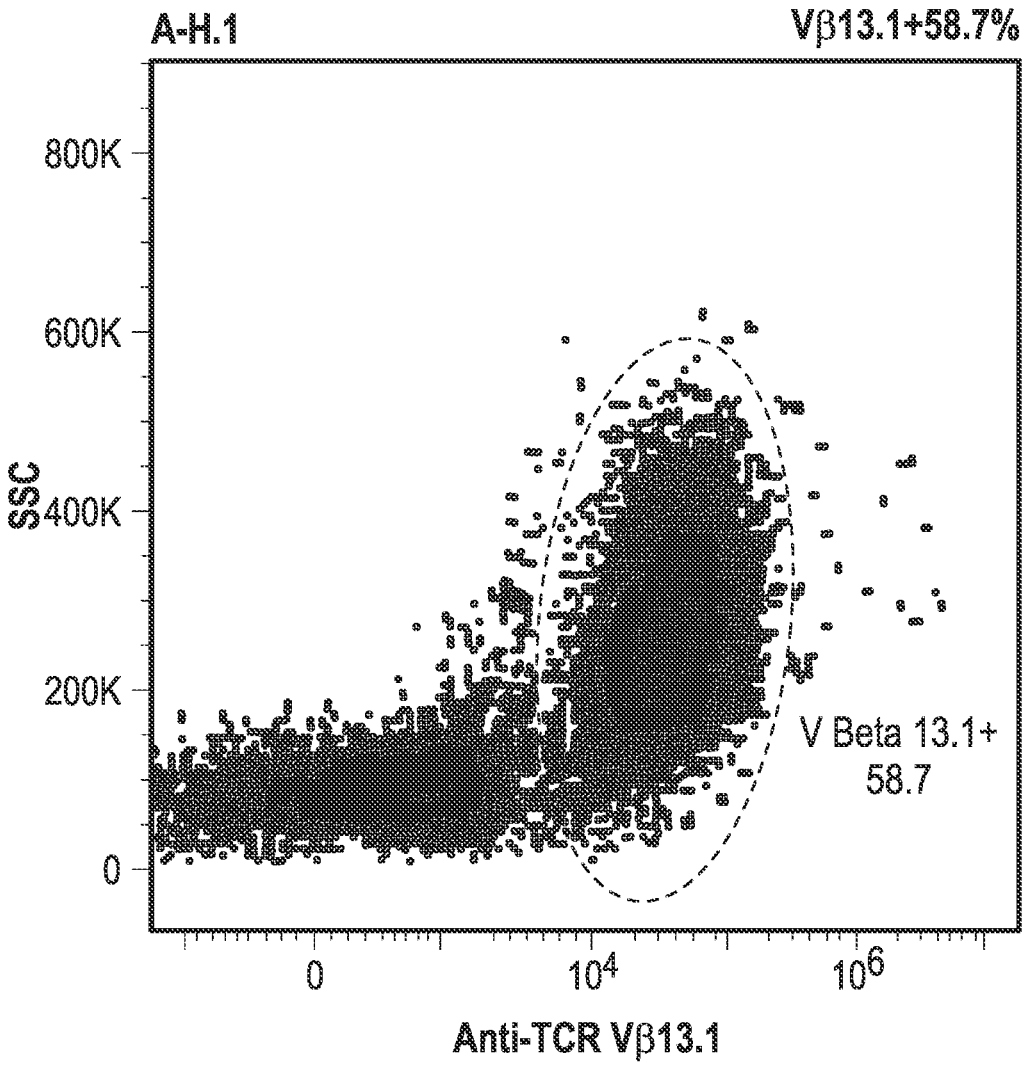


FIG. 4A
(Continued)

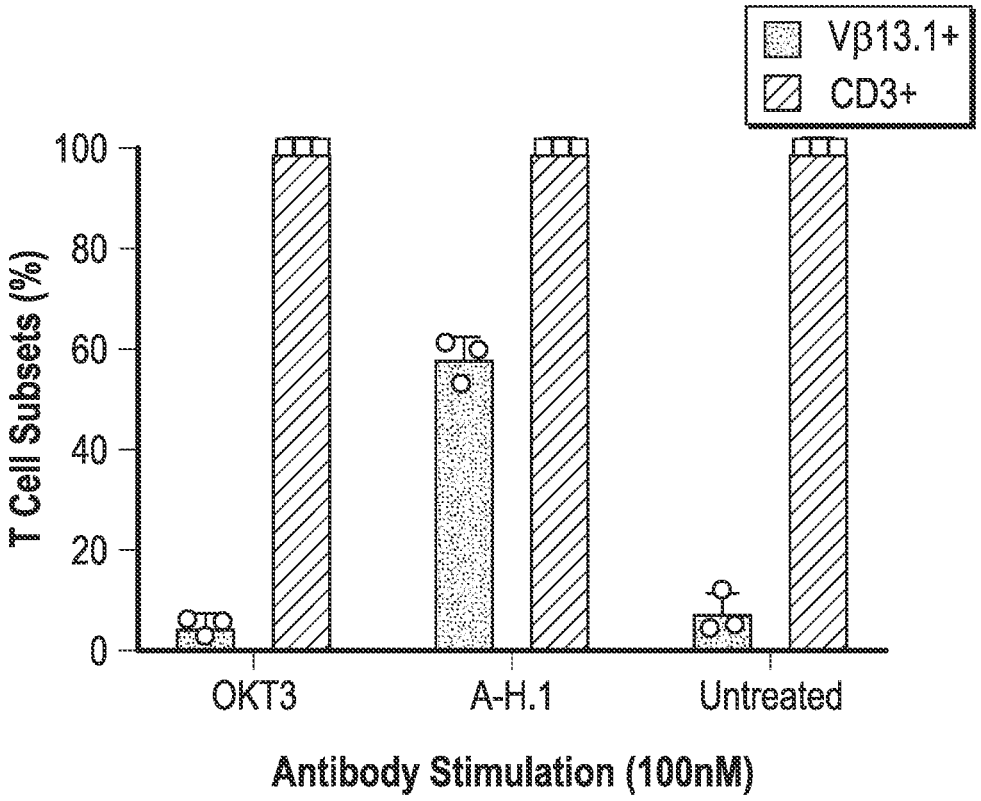

Vβ13.1+
CD3+
T Cell Subsets (%)
100
80
60
40
20
0
OKT3
A-H.1
Untreated
Antibody Stimulation (100nM)

FIG. 4B

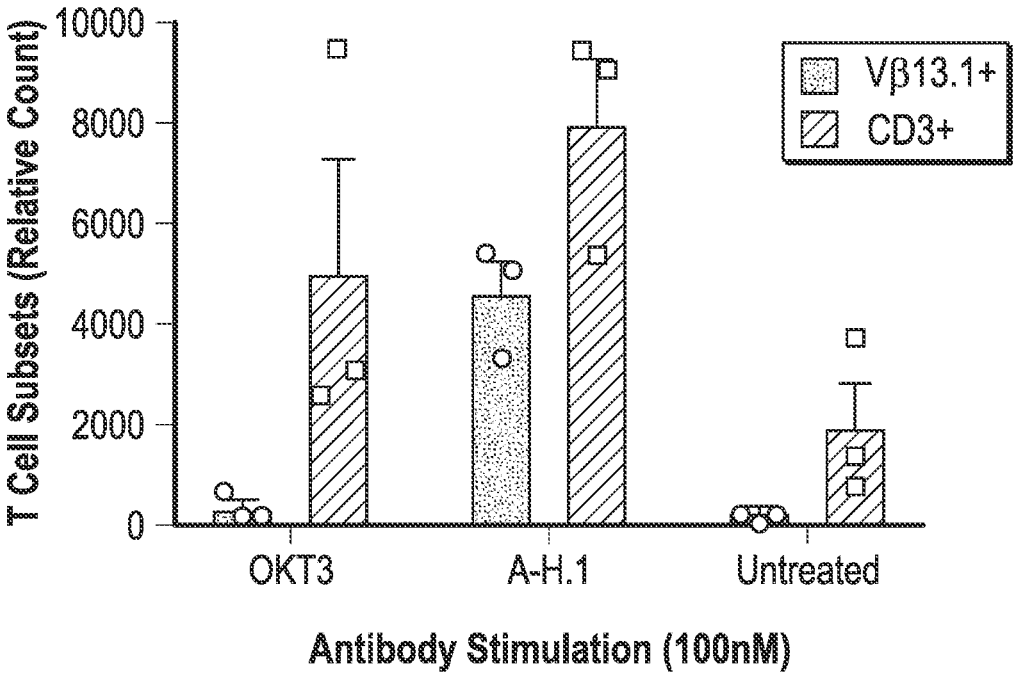

Vβ13.1+
CD3+
T Cell Subsets (Relative Count)
10000
8000
6000
4000
2000
0
OKT3
A-H.1
Untreated
Antibody Stimulation (100nM)

FIG. 4C

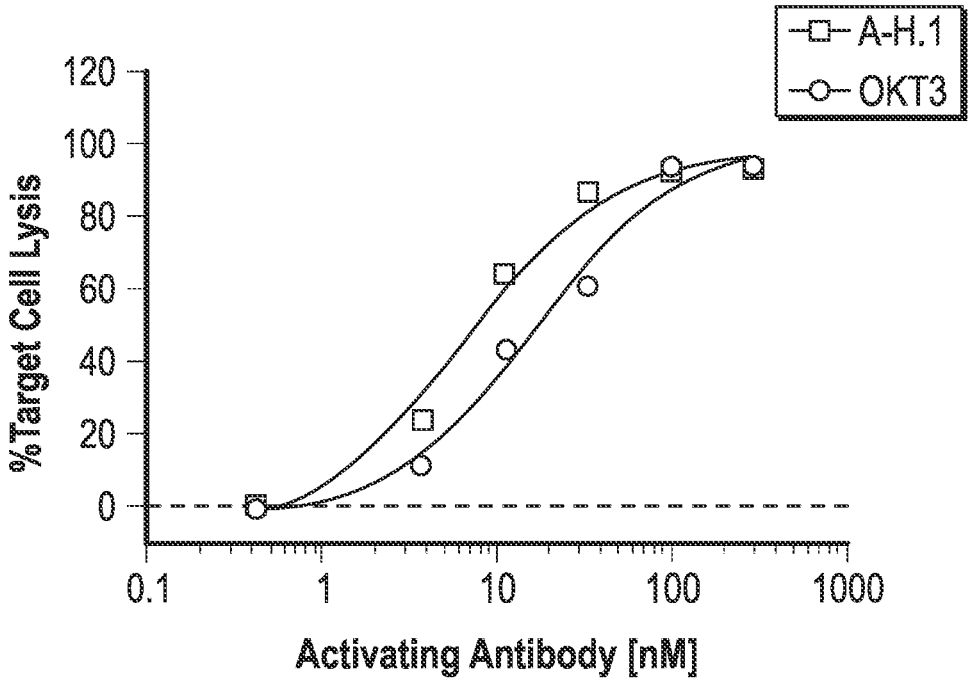

A-H.1
OKT3
120
100
80
60
40
20
0
% Target Cell Lysis
0.1
1
10
100
1000
Activating Antibody [nM]

FIG. 5A

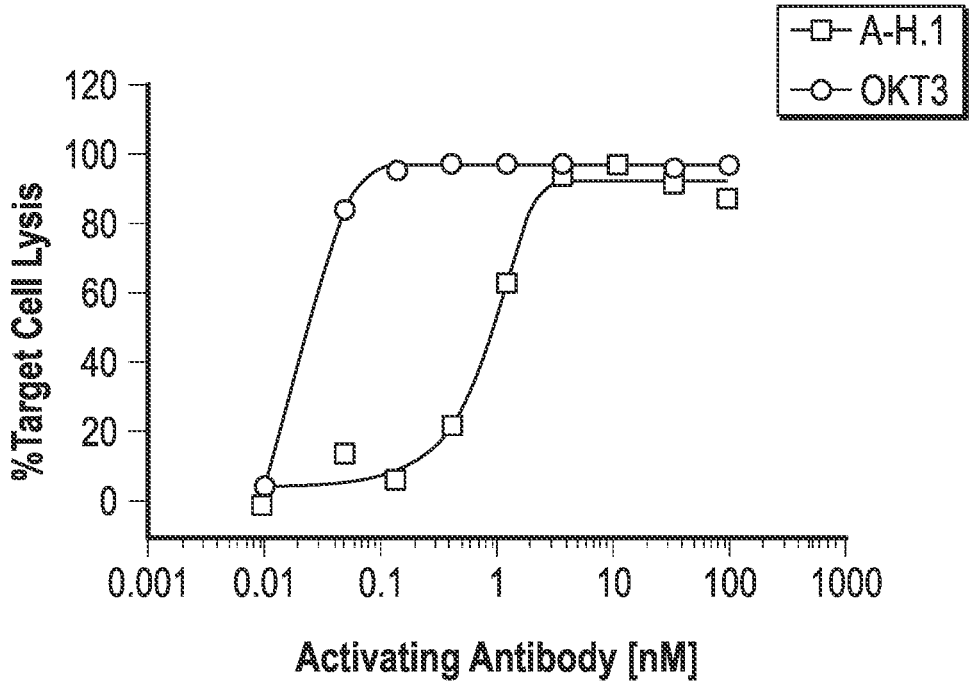

A-H.1
OKT3
120
100
80
60
40
20
0
% Target Cell Lysis
0.001
0.01
0.1
1
10
100
1000
Activating Antibody [nM]

FIG. 5B

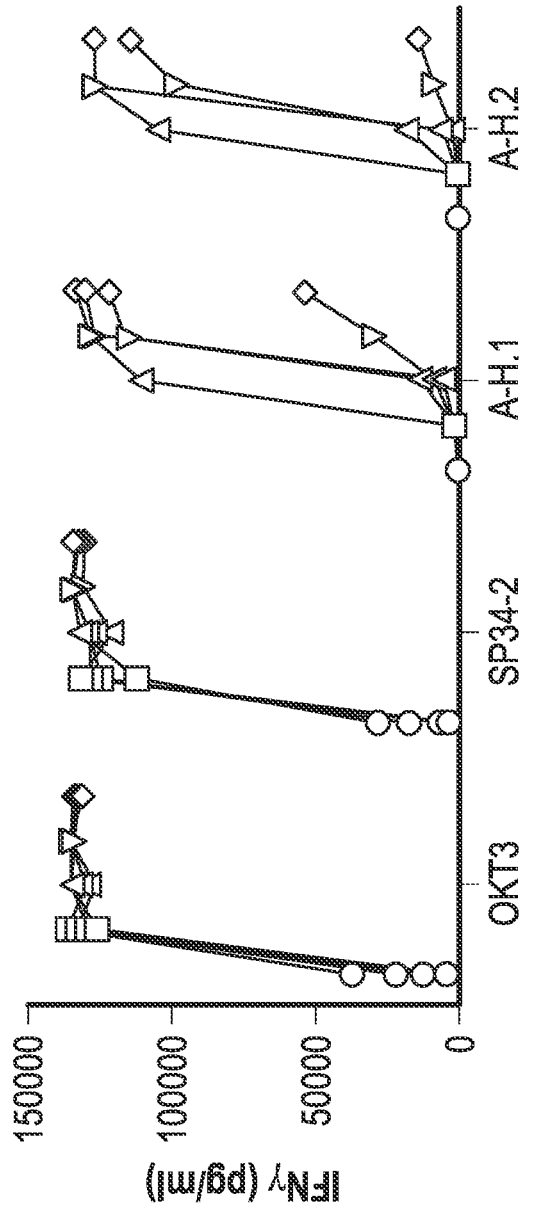


FIG. 6A

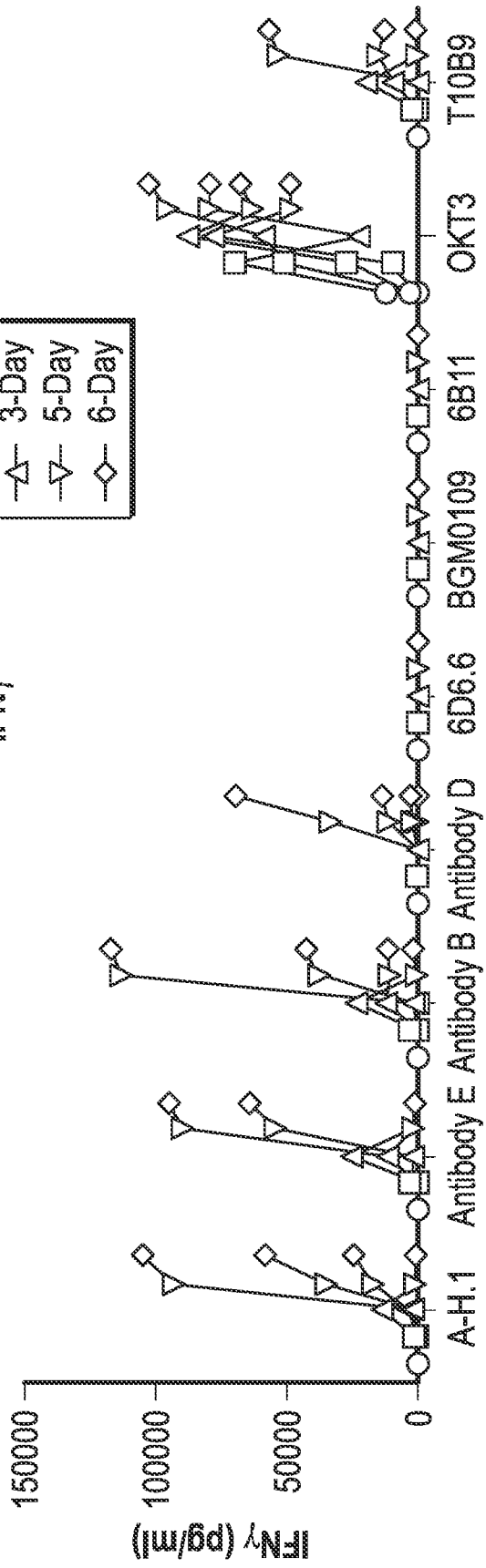

IFNγ
1-Day
2-Day
3-Day
5-Day
6-Day
IFNγ (pg/ml)
150000
100000
50000
0
A-H.1
Antibody E
Antibody B
Antibody D
6D6.6
BGM0109
6B11
OKT3
T10B9
Ab [100] nM

FIG. 6B

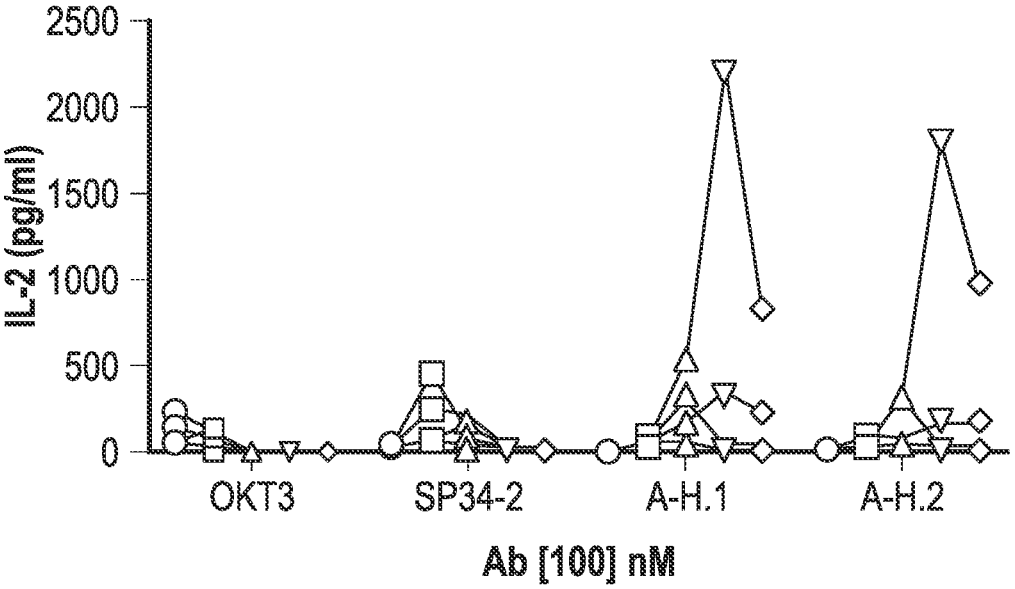


FIG. 7A

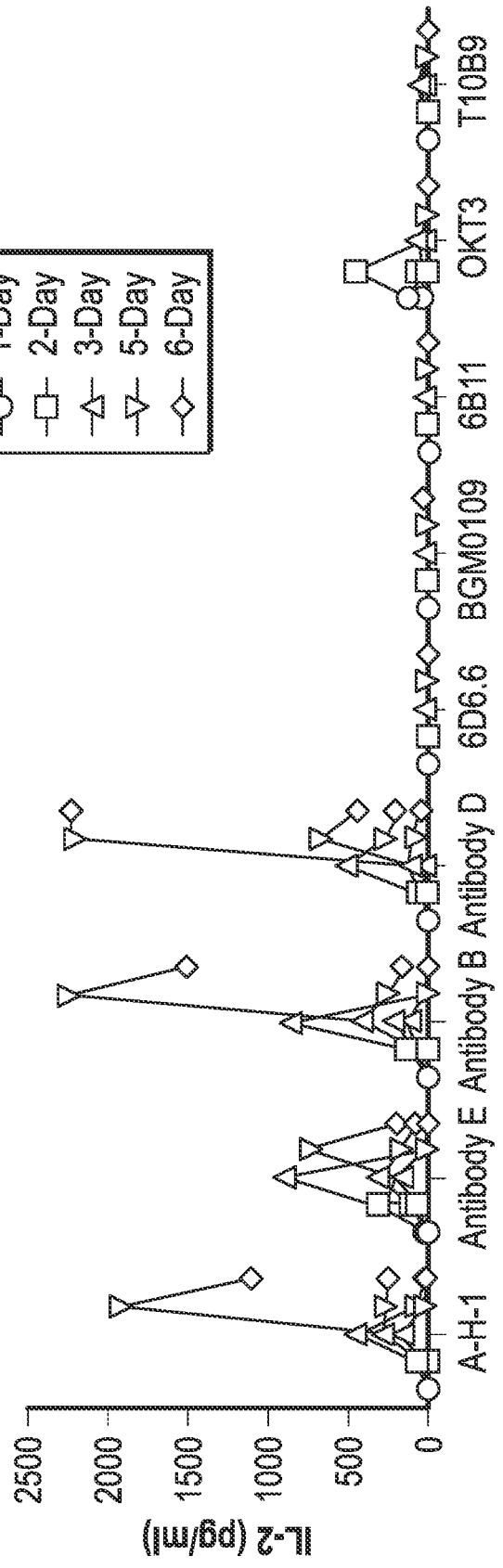

IL-2
1-Day
2-Day
3-Day
5-Day
6-Day
IL-2 (pg/ml)
2500
2000
1500
1000
500
0
A-H-1
Antibody E
Antibody B
Antibody D
6D6.6
BGM0109
6B11
OKT3
T10B9
Ab [100] nM

FIG. 7B

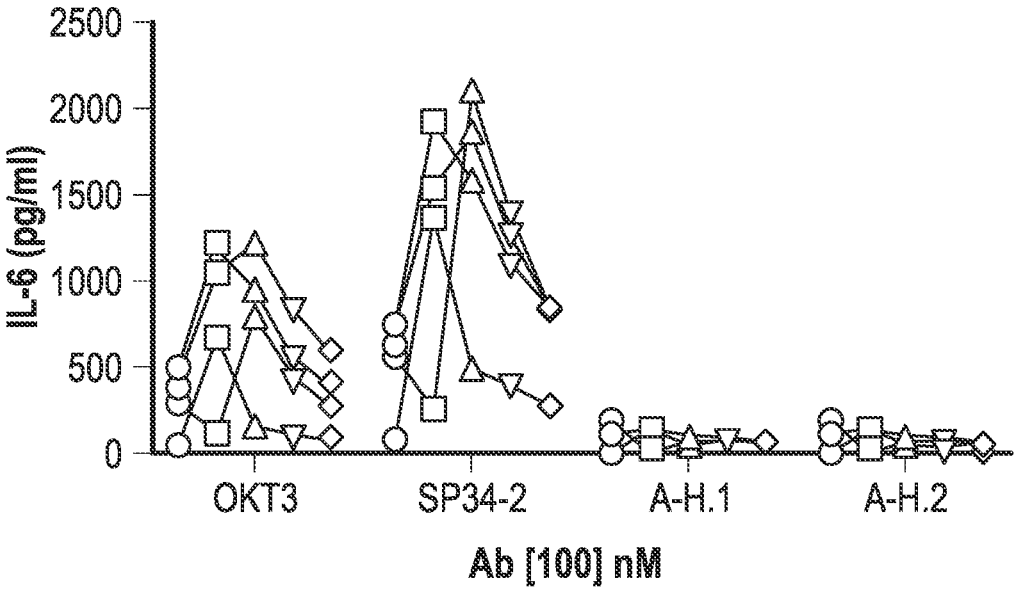


FIG. 8A

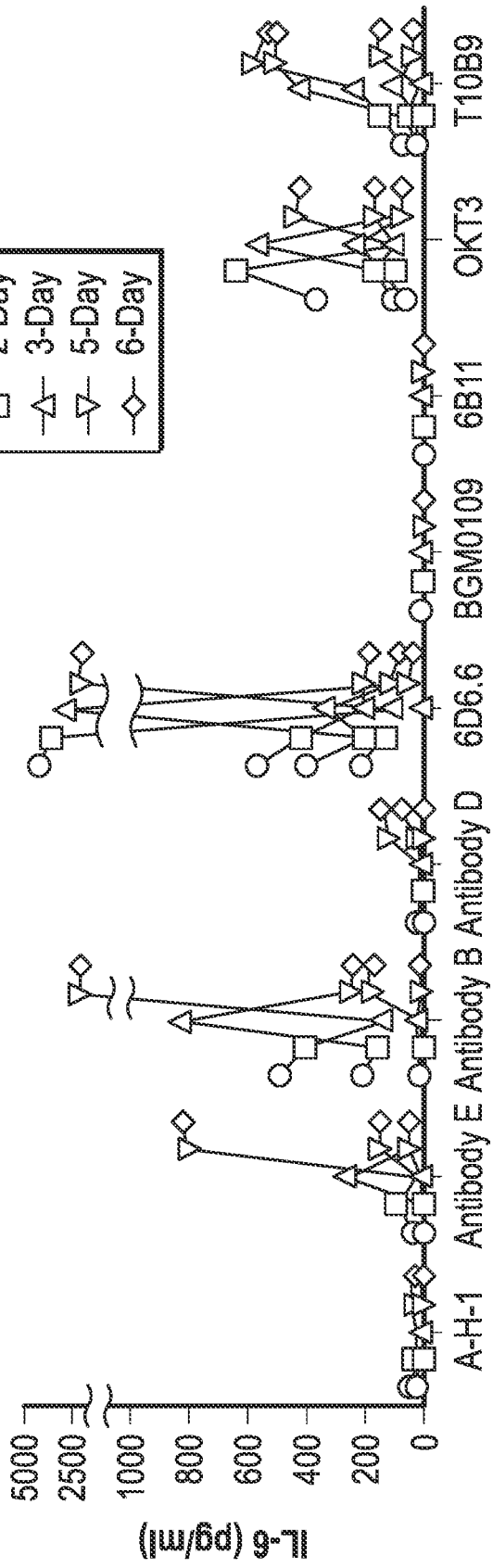

IL-6
1-Day
2-Day
3-Day
5-Day
6-Day
IL-6 (pg/ml)
5000
2500
1000
800
600
400
200
0
A-H-1
Antibody E
Antibody B
Antibody D
6D6.6
BGM0109
6B11
OKT3
T10B9
Ab [100] nM

FIG. 8B

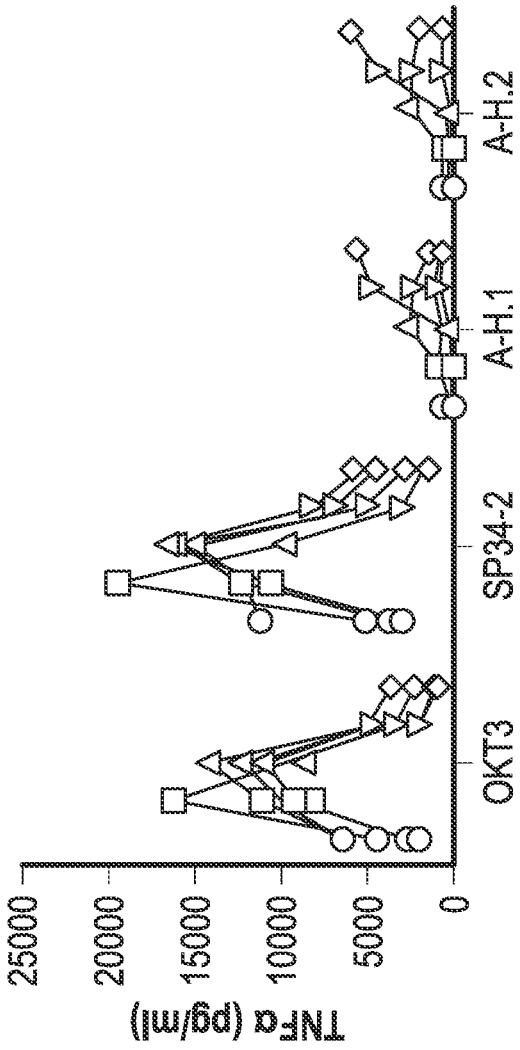

TNFα (pg/ml)
25000
20000
15000
10000
5000
0
OKT3
SP34-2
A-H.1
A-H.2
Ab [100] nM

FIG. 9A

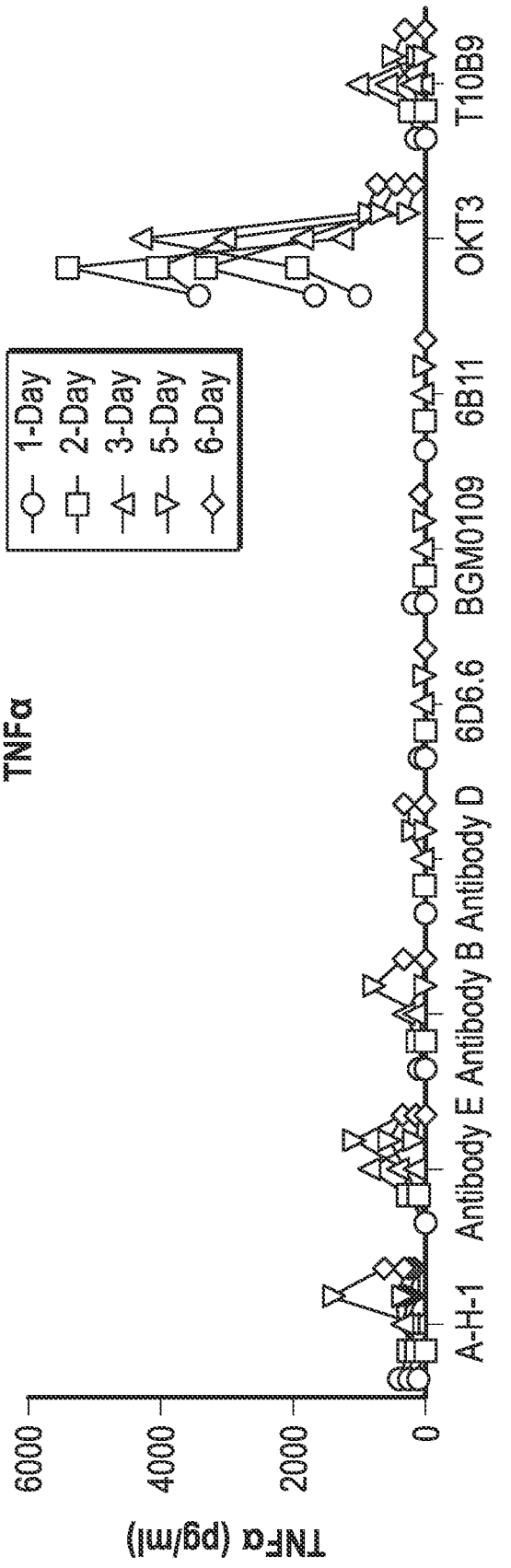

TNFα
1-Day
2-Day
3-Day
5-Day
6-Day
TNFα (pg/ml)
6000
4000
2000
0
A-H-1
Antibody E
Antibody B
Antibody D
6D6.6
BGM0109
6B11
OKT3
T10B9
Ab [100] nM

FIG. 9B

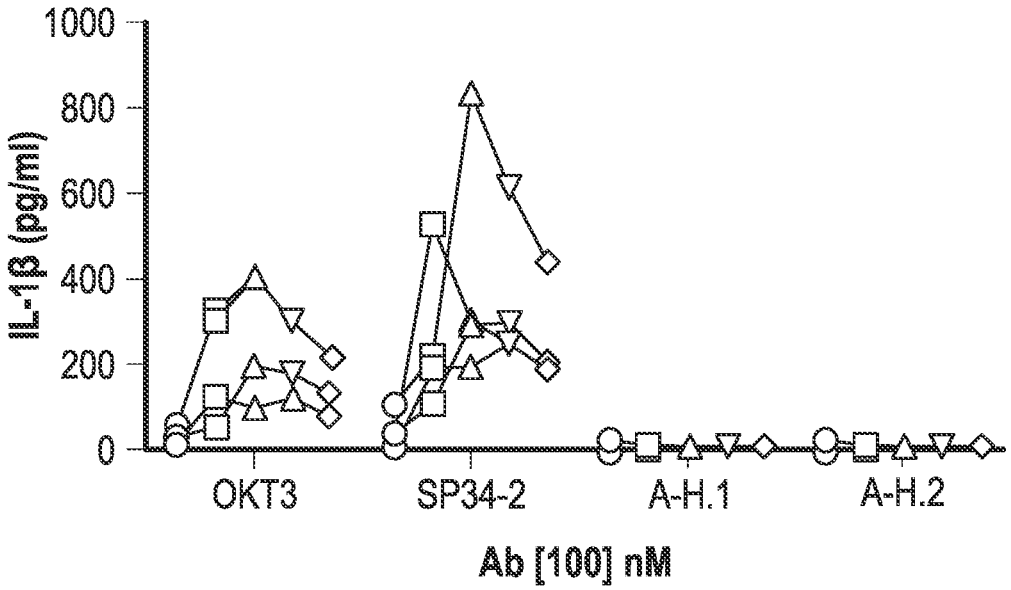


FIG. 10A

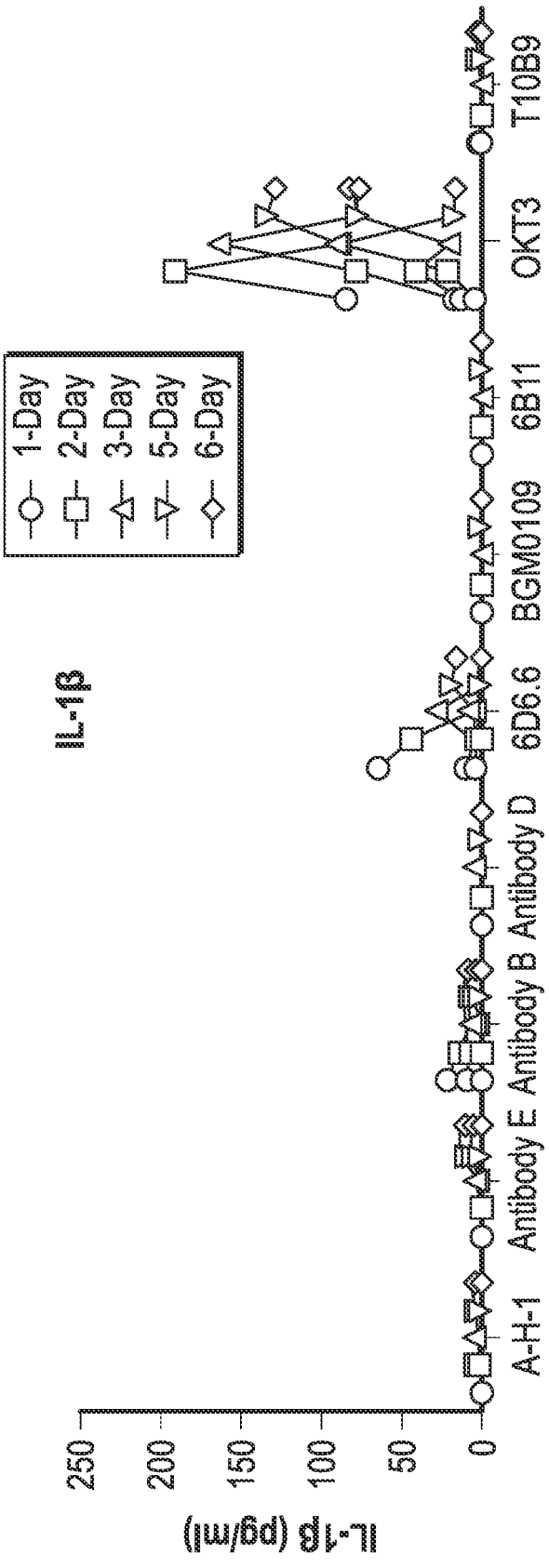

IL-1β
1-Day
2-Day
3-Day
5-Day
6-Day
IL-1β (pg/ml)
250
200
150
100
50
0
A-H-1
Antibody E
Antibody B
Antibody D
6D6.6
BGM0109
6B11
OKT3
T10B9
Ab [100] nm

FIG. 10B

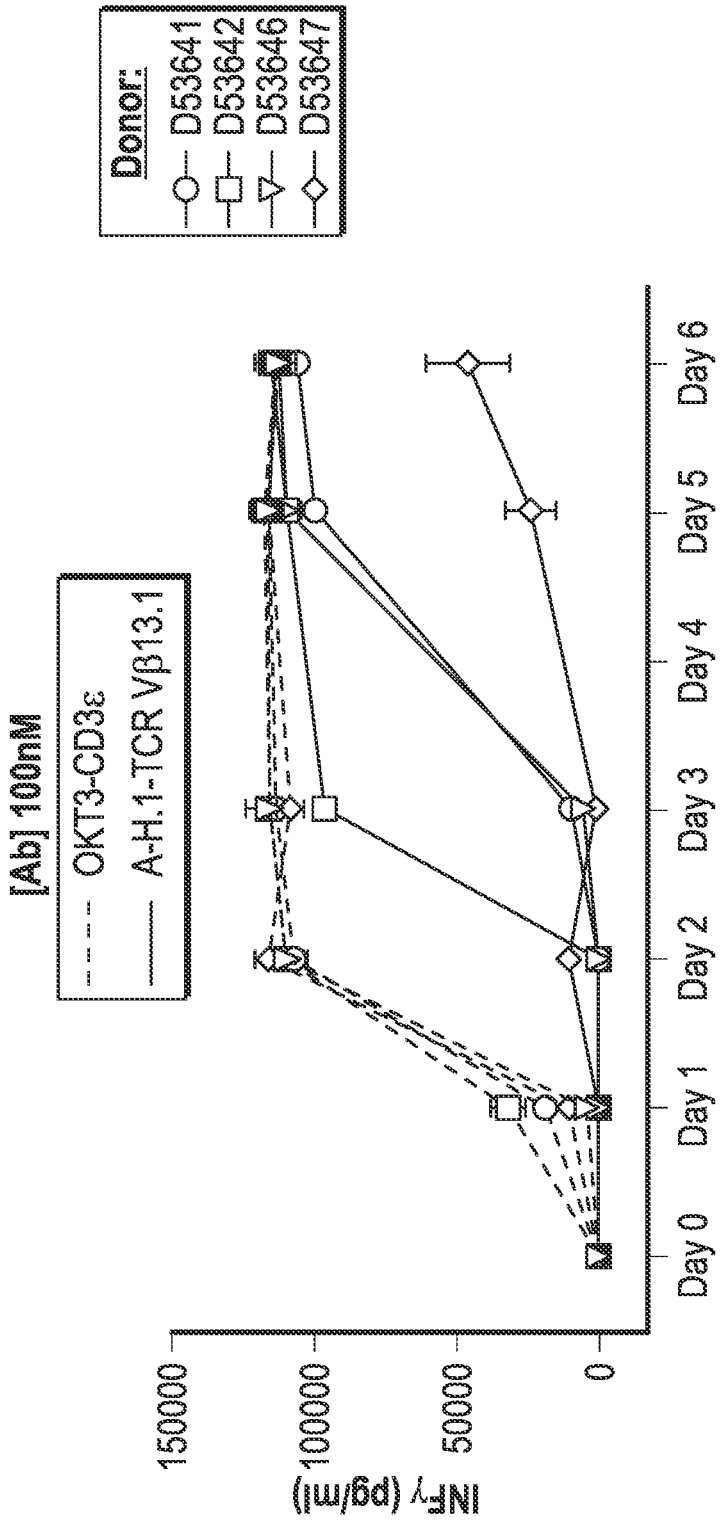

Donor:
D53641
D53642
D53646
D53647
[Ab] 100nM
OKT3-CD3ε
A-H.1-TCR Vβ13.1
INFγ (pg/ml)
150000
100000
50000
0
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Time (Day)

FIG. 11A

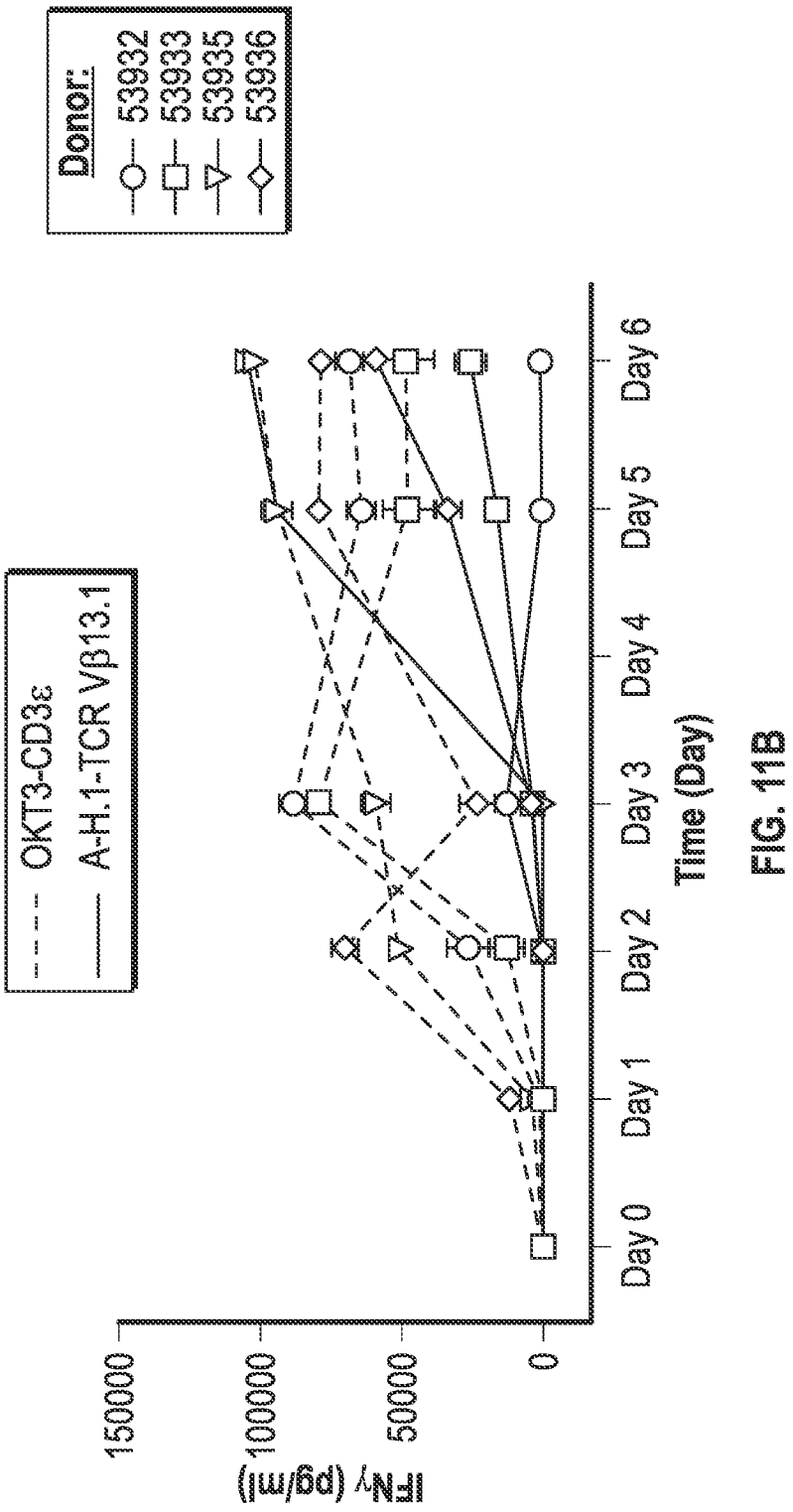

Donor:
53932
53933
53935
53936
OKT3-CD3ε
A-H.1-TCR Vβ13.1
IFNγ (pg/ml)
150000
100000
50000
0
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Time (Day)

FIG. 11B

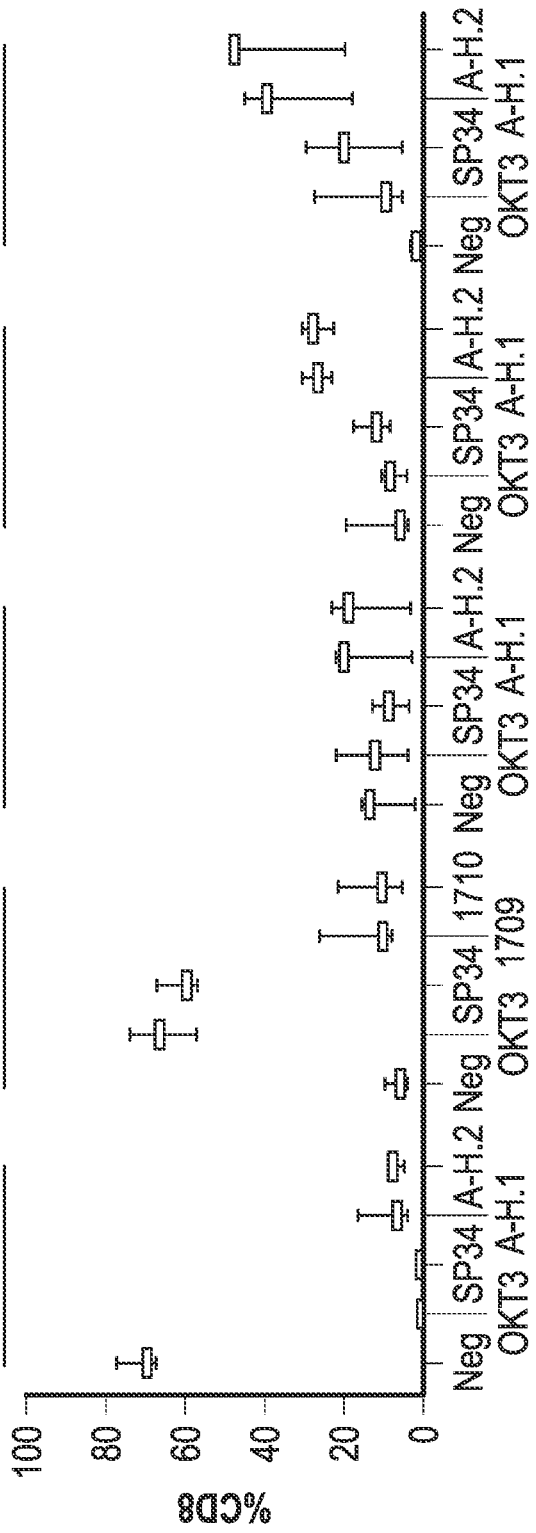

%CD8
100
80
60
40
20
0
Naïve
Tcm
Tem
Temra
TSCM
Neg
SP34
A-H.2
A-H.1
OKT3
1709
1710
Log [Ab] 100nM

FIG. 12

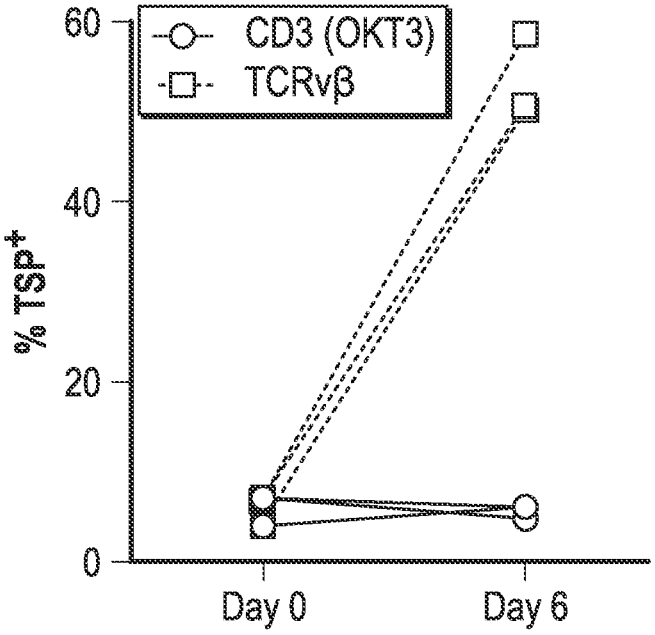


FIG. 13A

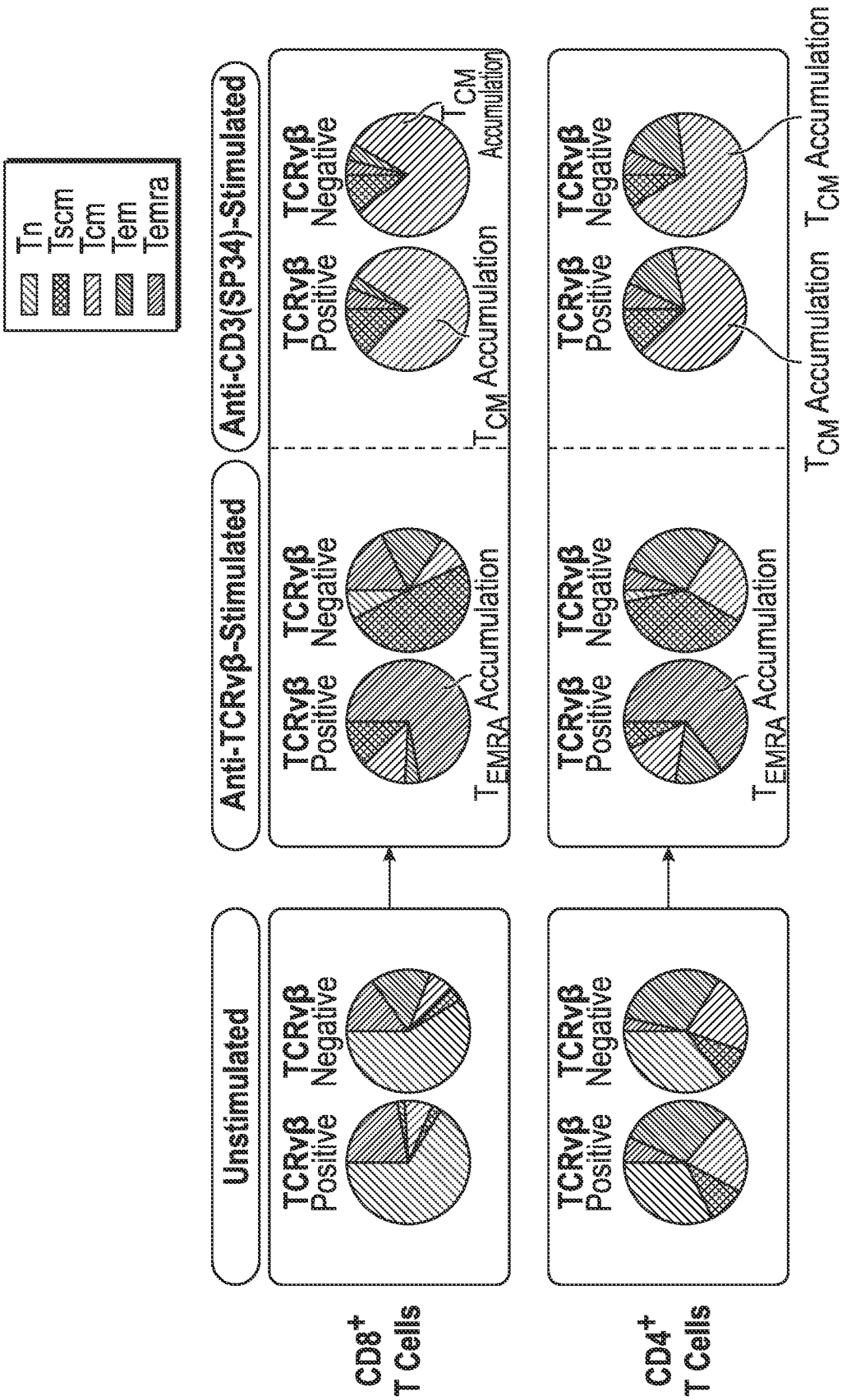

Tn
Tscm
Tcm
Tem
Temra
Unstimulated
Anti-TCRvβ-Stimulated
Anti-CD3(SP34)-Stimulated
TCRvβ Positive
TCRvβ Negative
TEMRA Accumulation
TCM Accumulation
CD8+ T Cells
CD4+ T Cells

FIG. 13B

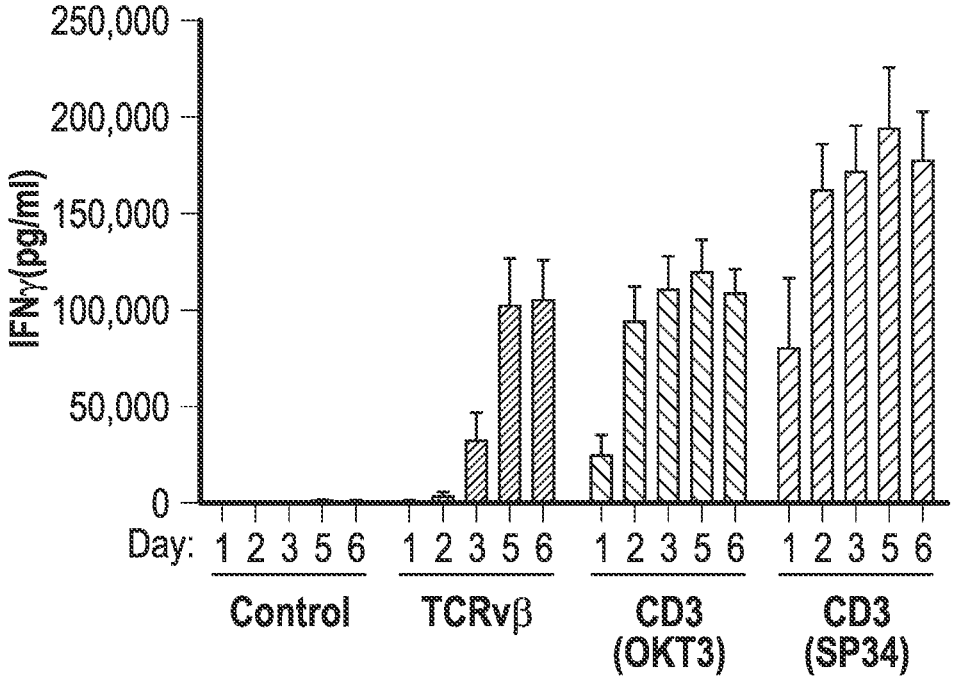


FIG. 13C

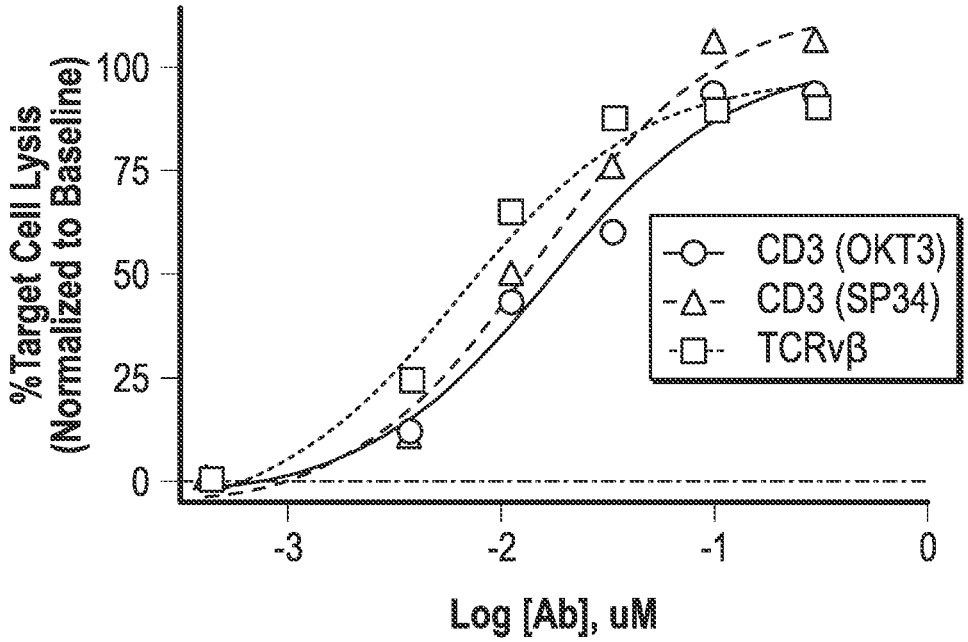


FIG. 13D

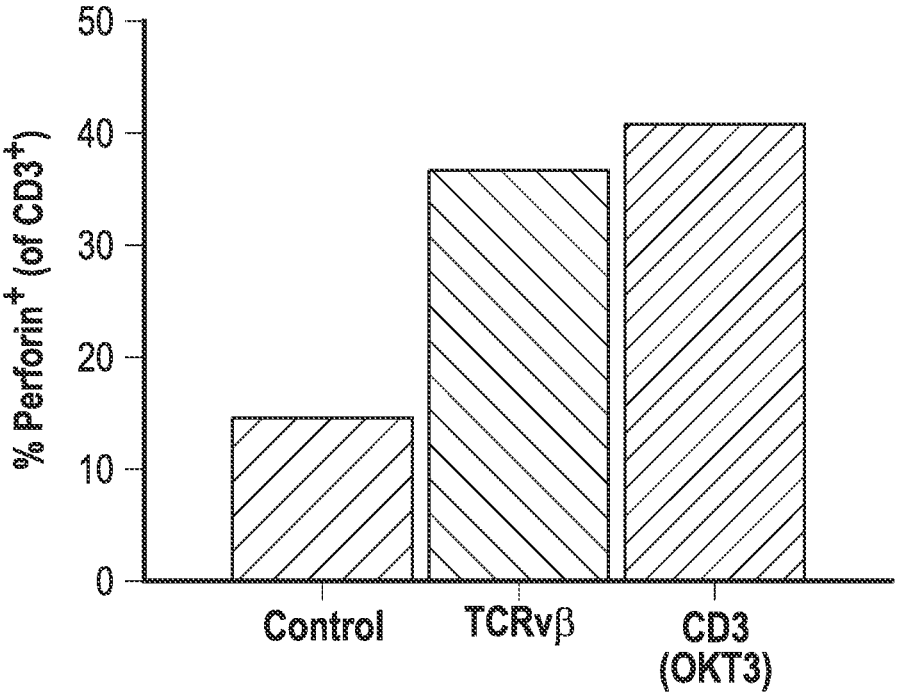


FIG. 13E

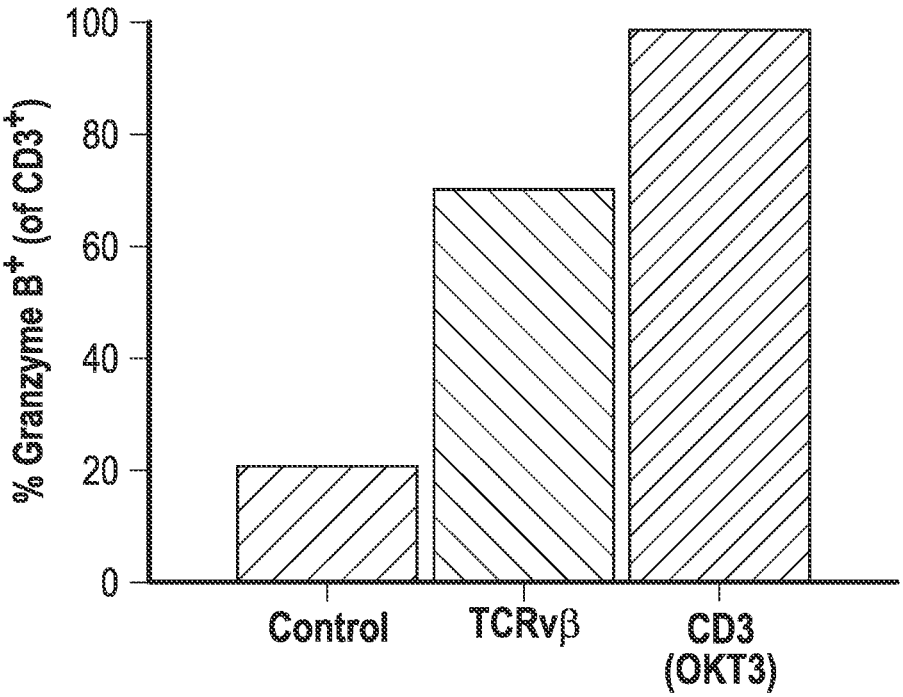
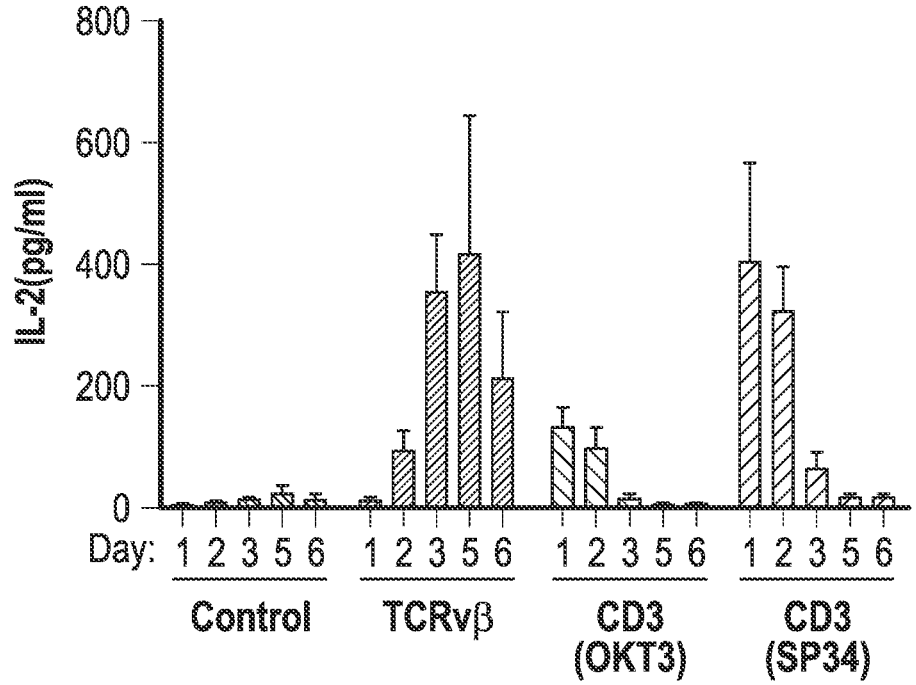


FIG. 13F


800
600
400
200
0
IL-2(pg/ml)
Day: 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6
Control
TCRvβ
CD3 (OKT3)
CD3 (SP34)

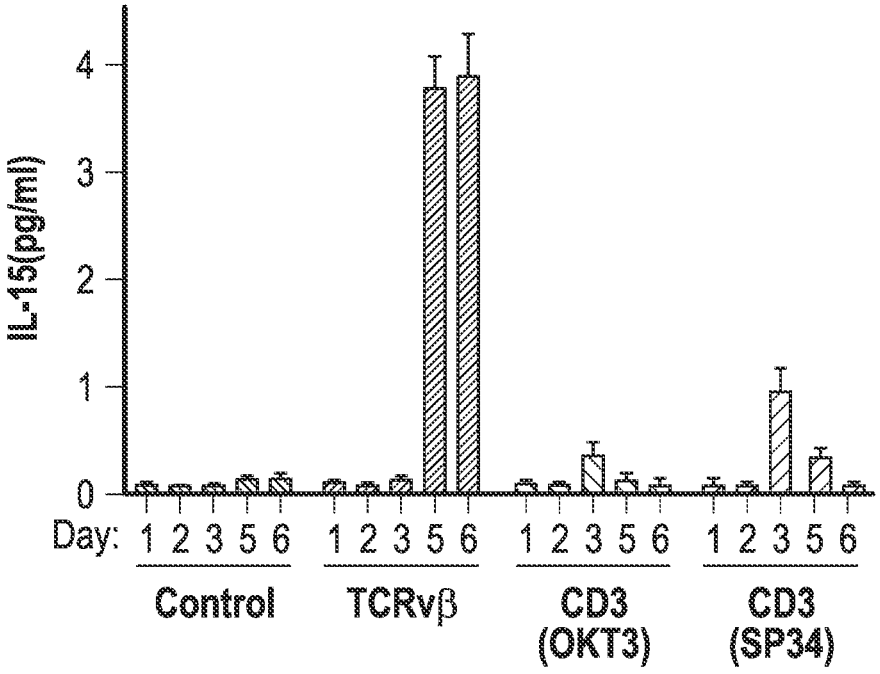

4
3
2
1
0
IL-15(pg/ml)
Day: 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6
Control
TCRvβ
CD3 (OKT3)
CD3 (SP34)

FIG. 14A

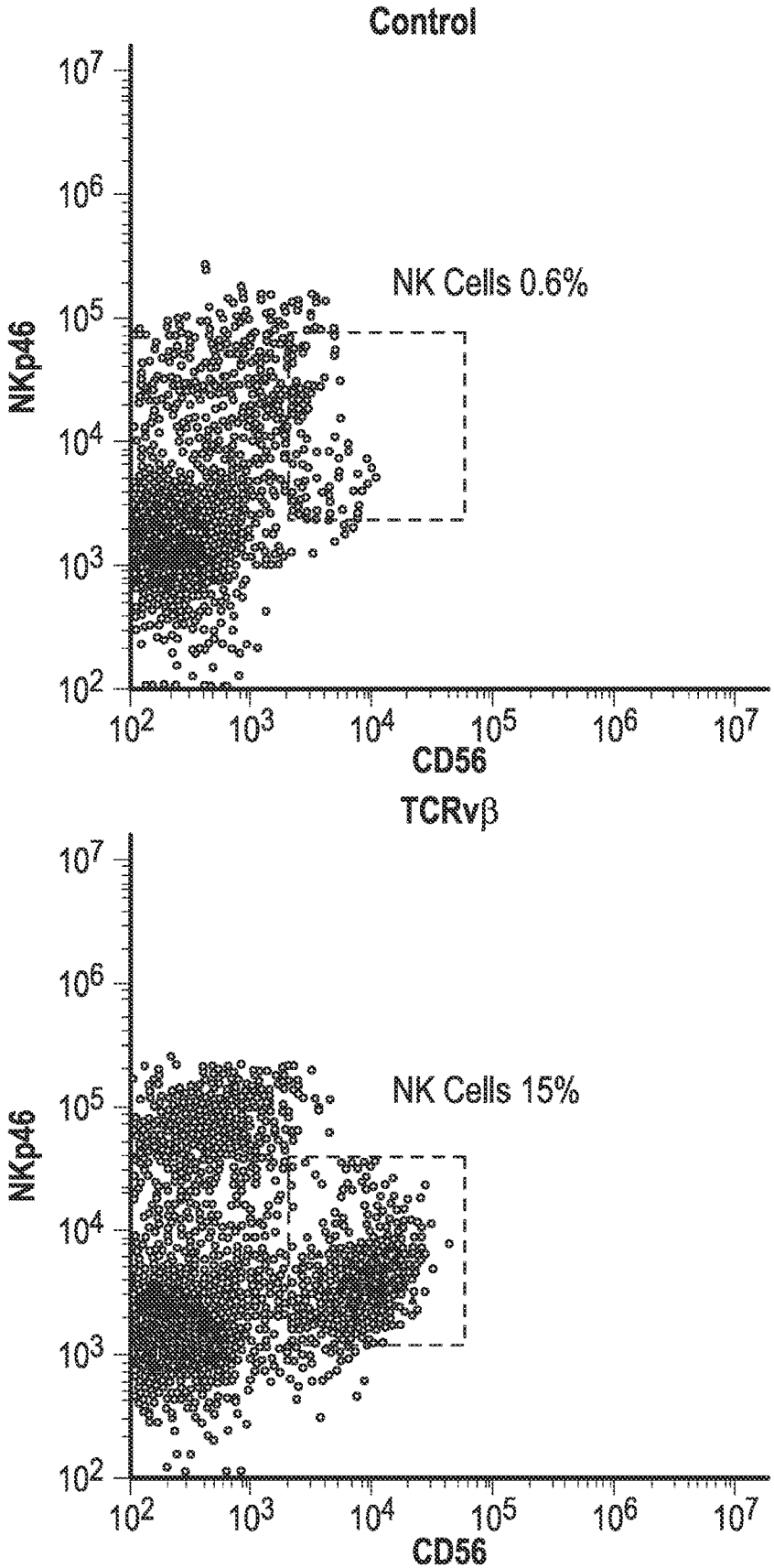


FIG. 14B

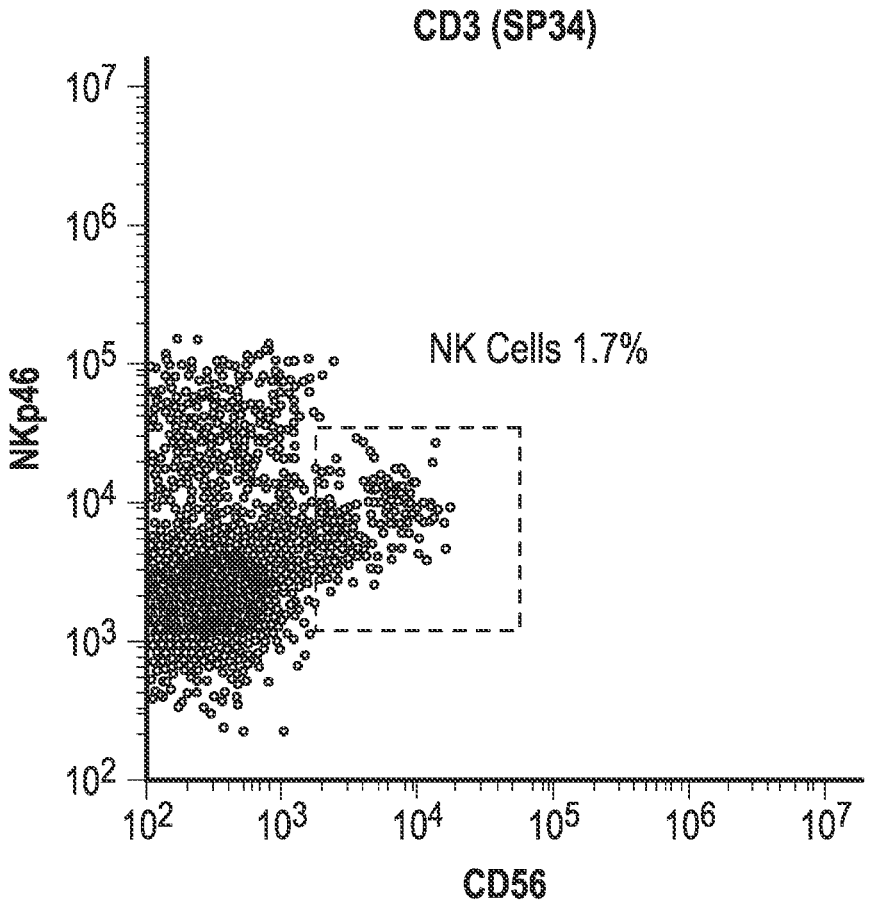


FIG. 14B
(Continued)

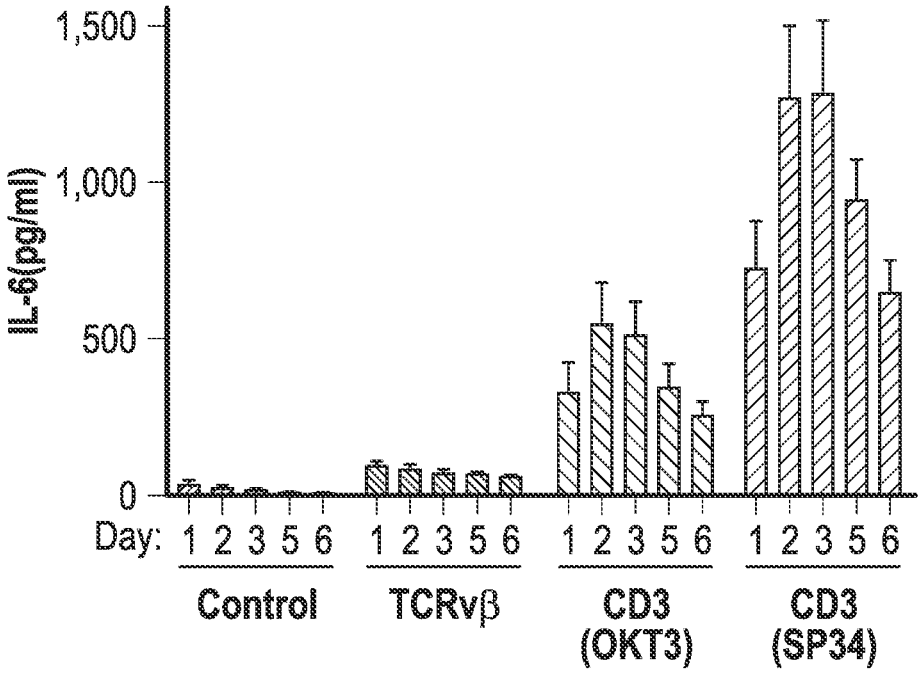


FIG. 15A

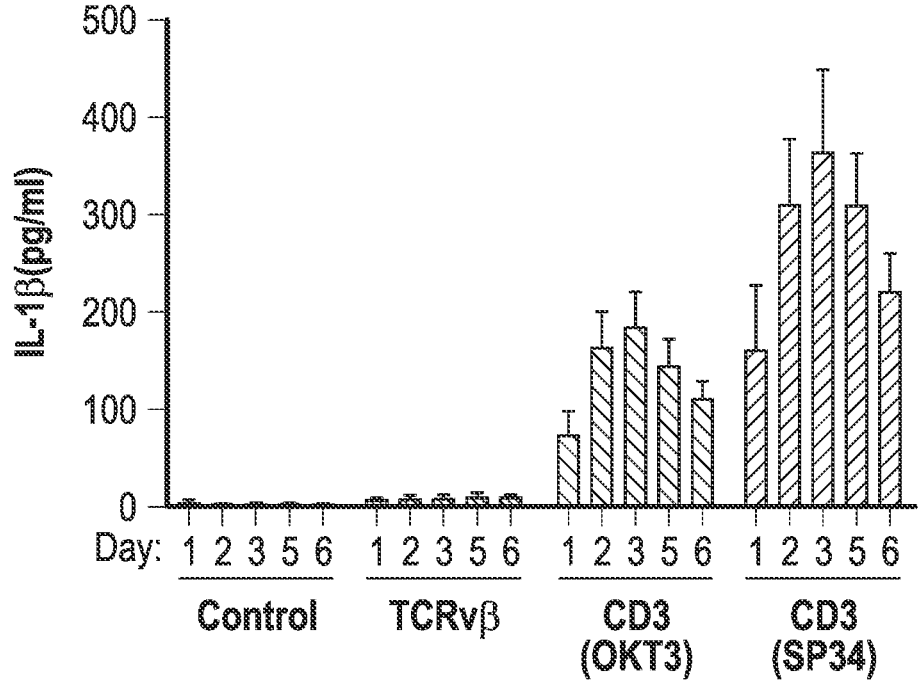


FIG. 15B

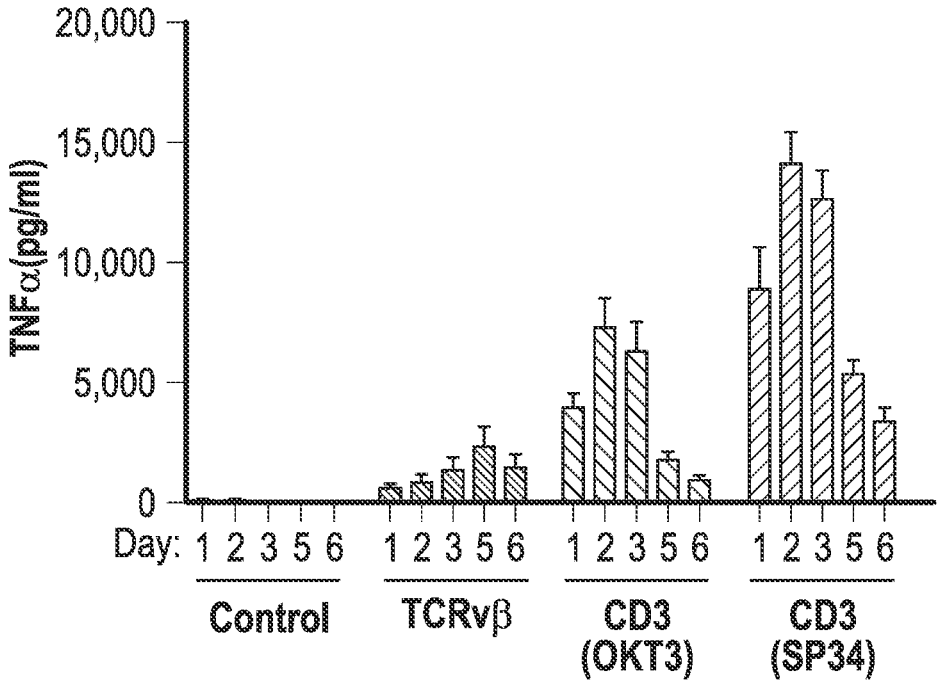

20,000
15,000
10,000
5,000
0
TNFα(pg/ml)
Day: 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6 1 2 3 5 6
Control
TCRvβ
CD3 (OKT3)
CD3 (SP34)

FIG. 15C

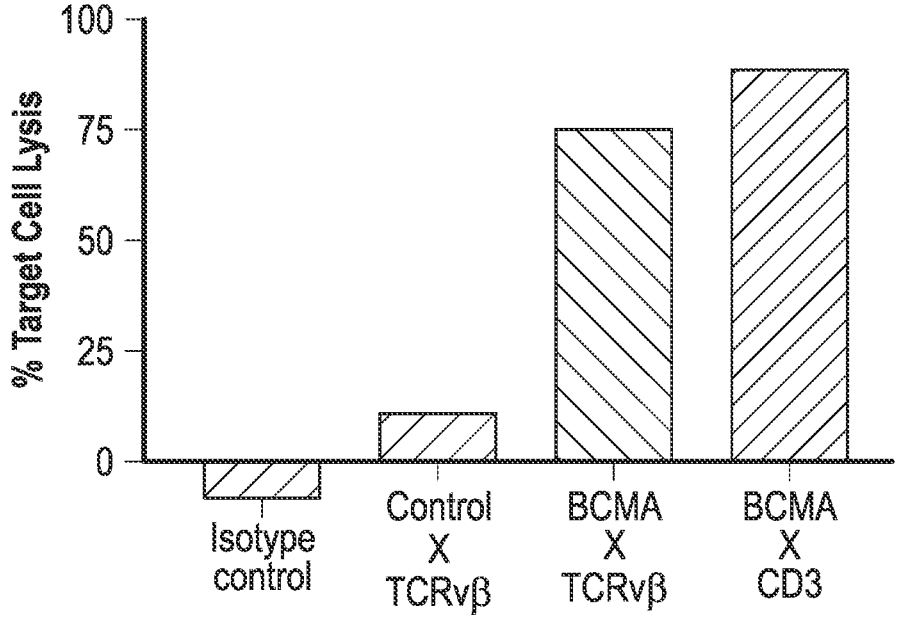


FIG. 16A

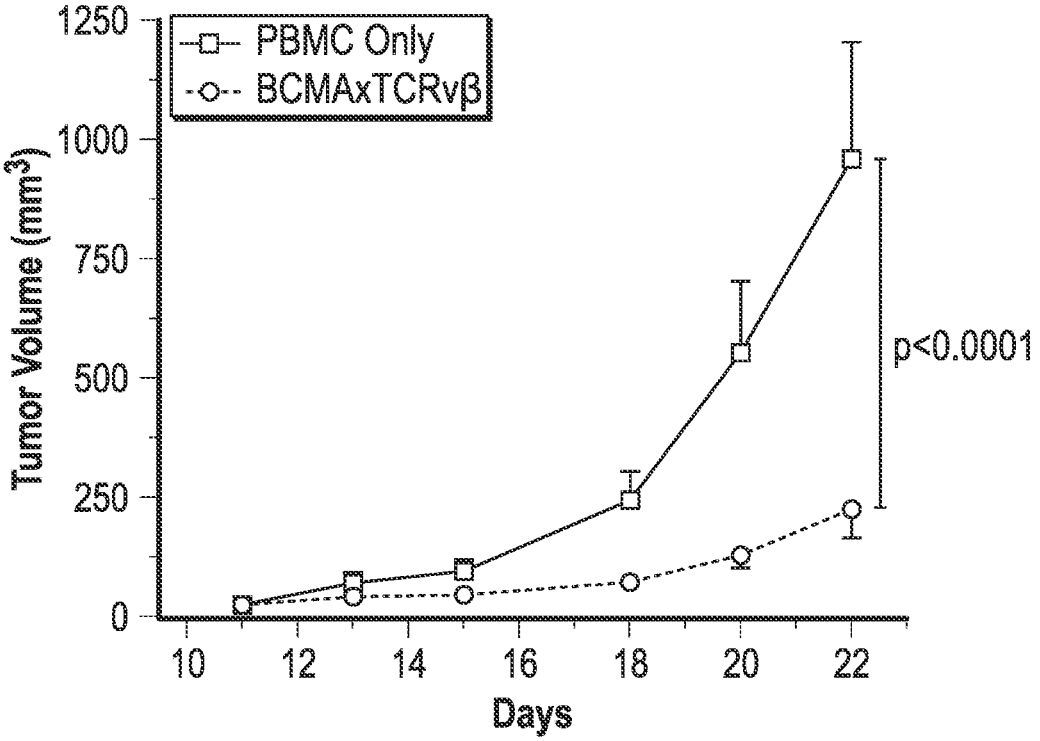


FIG. 16B

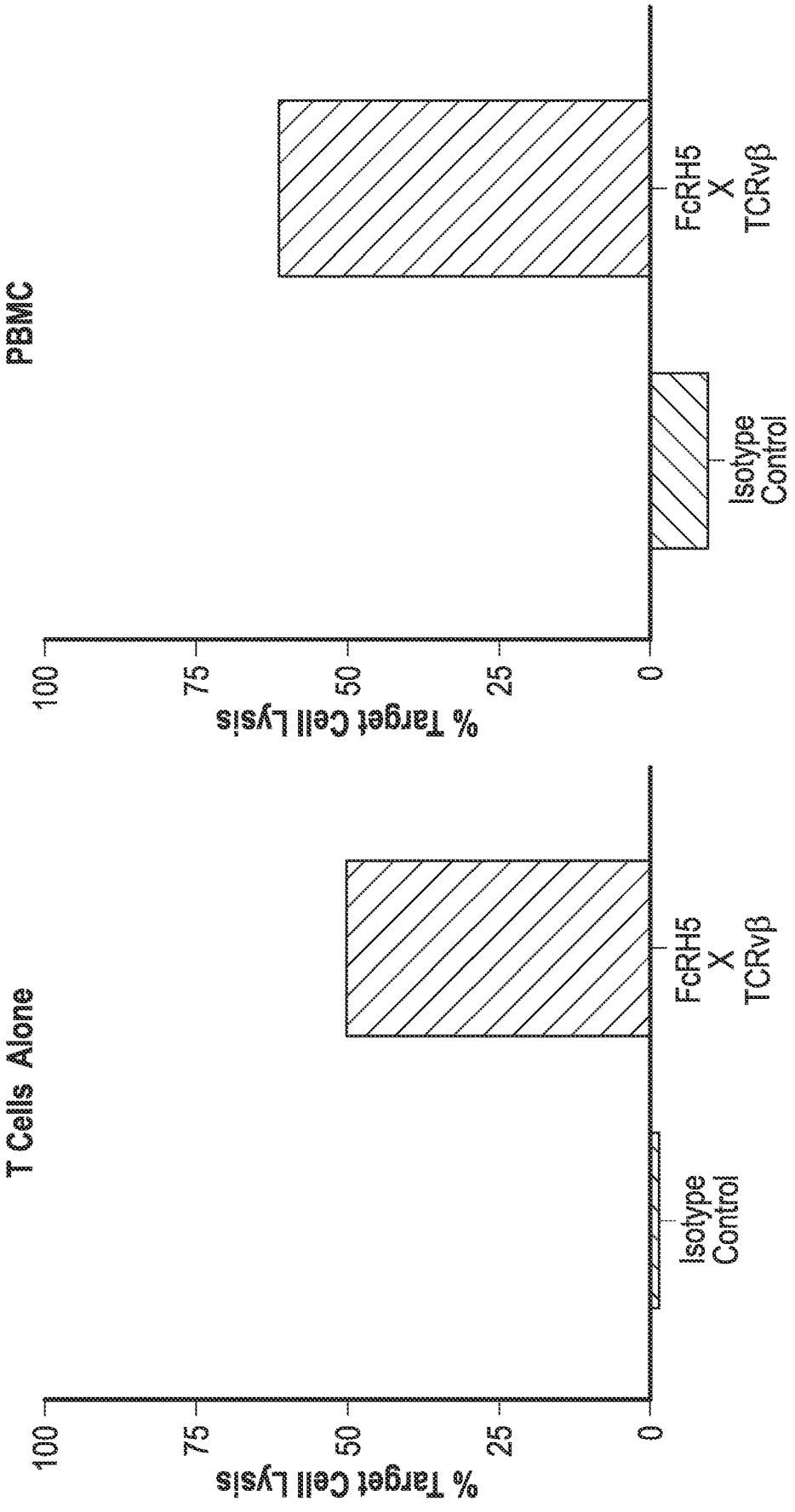

PBMC
% Target Cell Lysis
100
75
50
25
0
FcRH5 X TCRvβ
Isotype Control
T Cells Alone
% Target Cell Lysis
100
75
50
25
0
FcRH5 X TCRvβ
Isotype Control

FIG. 17

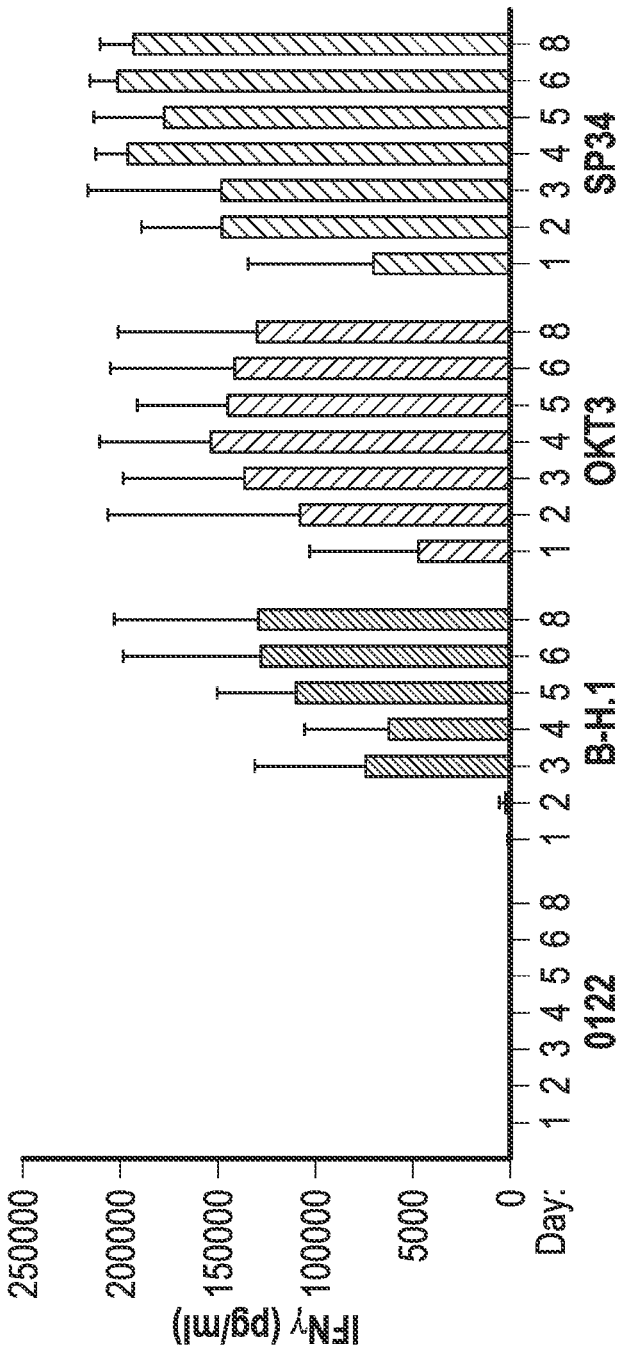

IFNγ (pg/ml)
250000
200000
150000
100000
5000
0
Day:
0122
B-H.1
OKT3
SP34
Ab [100] nM

FIG. 18A

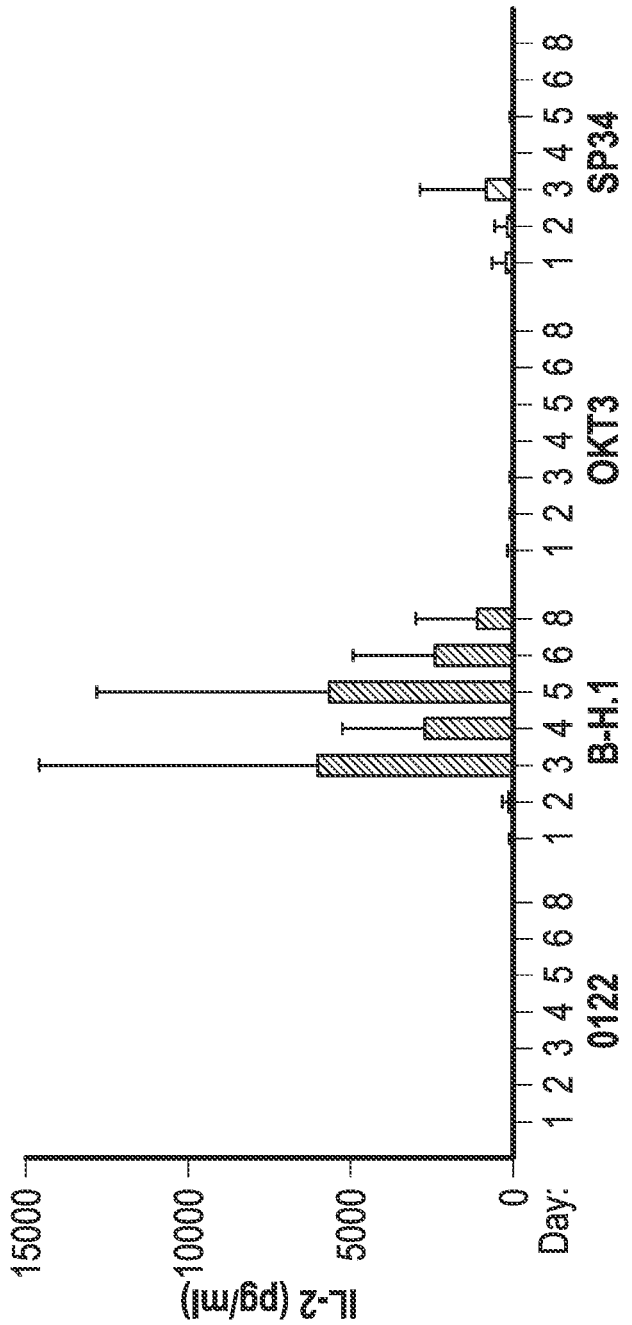


FIG. 18B

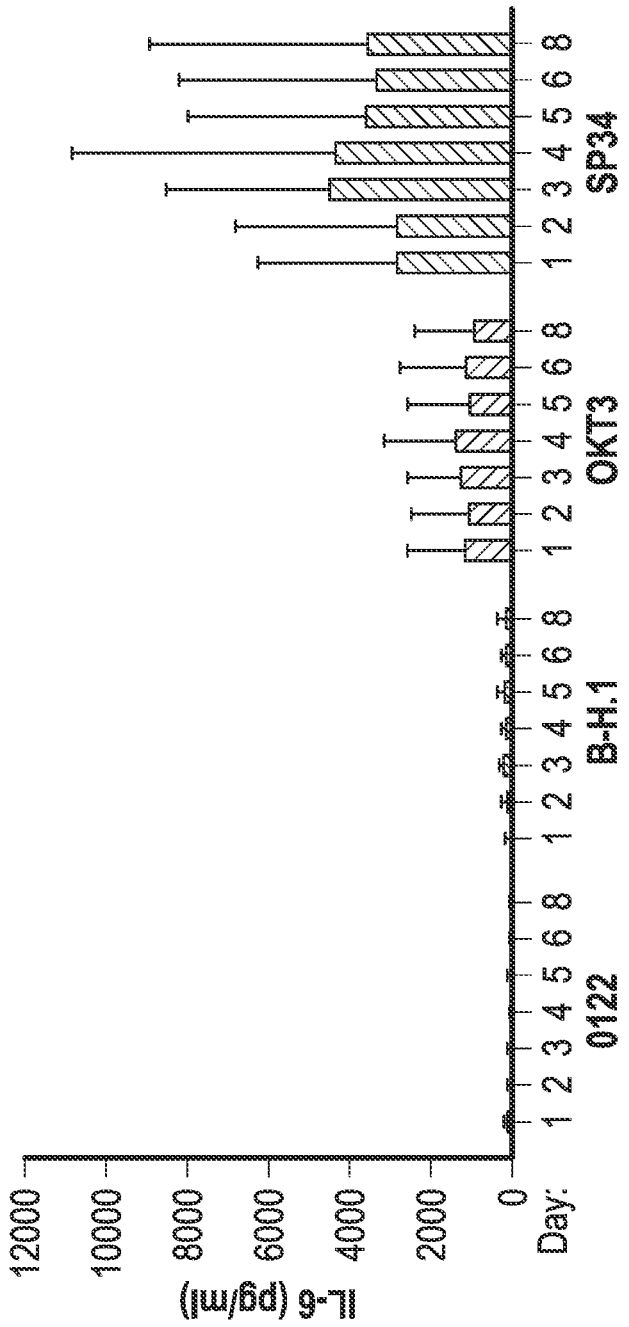

IL-6 (pg/ml)
12000
10000
8000
6000
4000
2000
0
Day:
0122
B-H.1
OKT3
SP34
Ab [100] nM

FIG. 19A

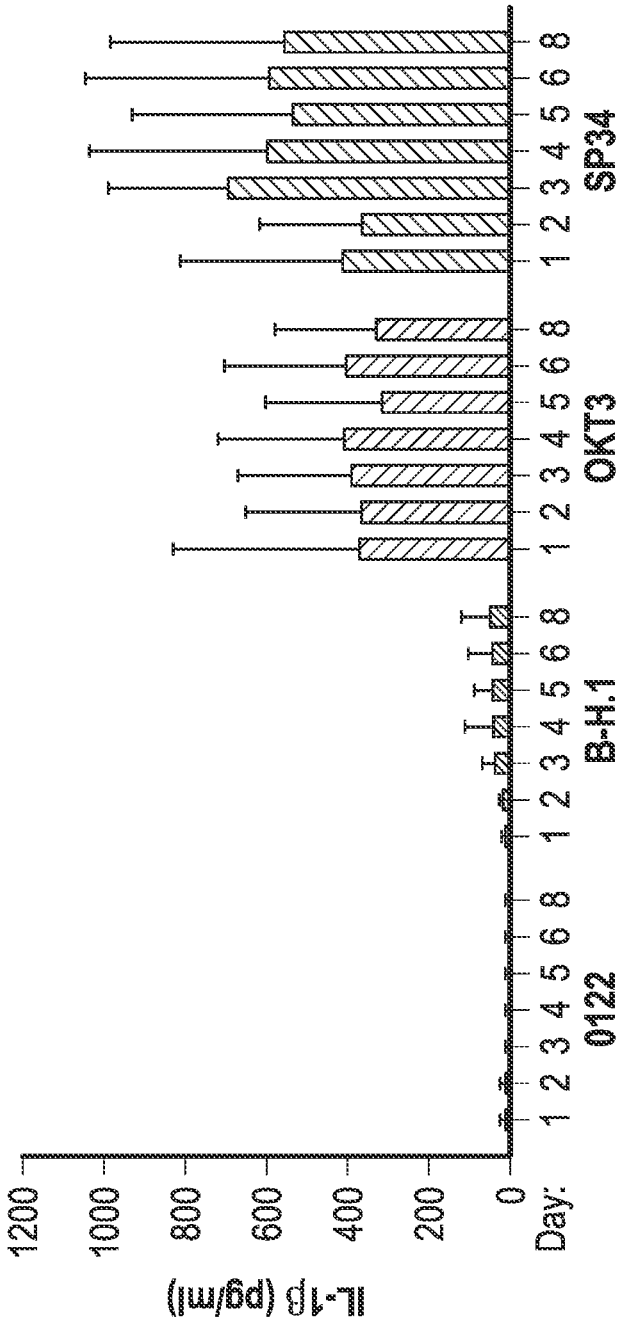

IL-1β (pg/ml)
1200
1000
800
600
400
200
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
B-H.1
OKT3
SP34
Ab [100] nM

FIG. 19B

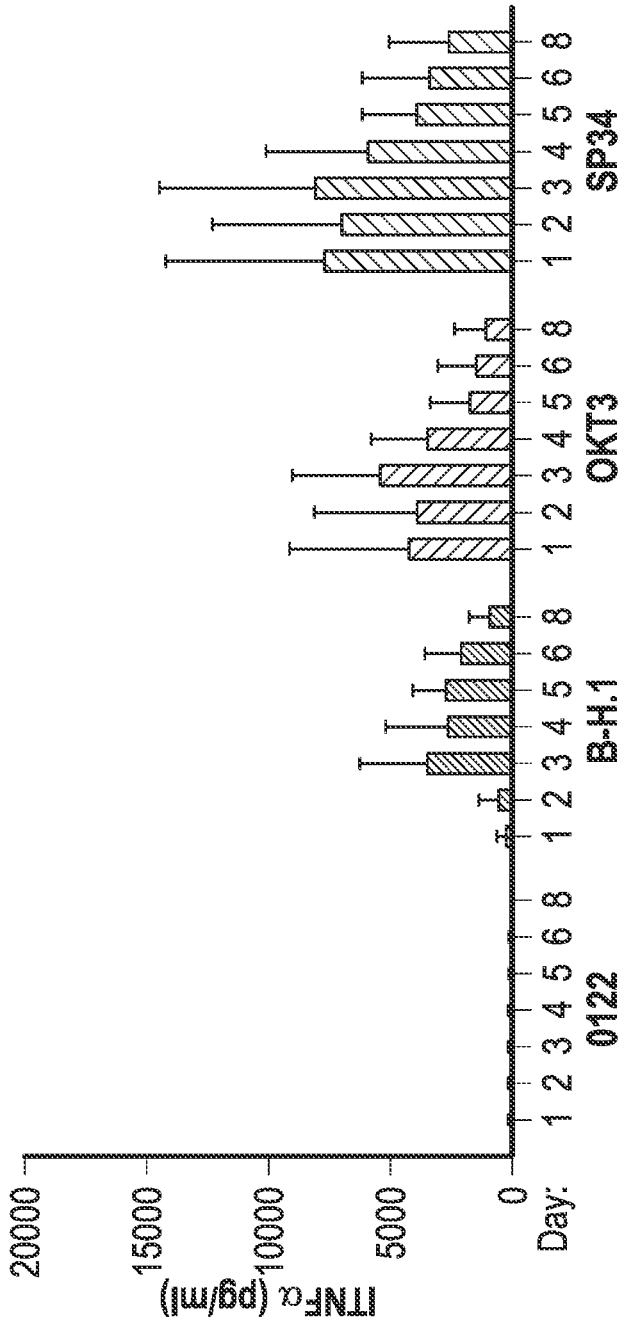

TNFα (pg/ml)
20000
15000
10000
5000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
OKT3
1 2 3 4 5 6 8
SP34
Ab [100] nM

FIG. 19C

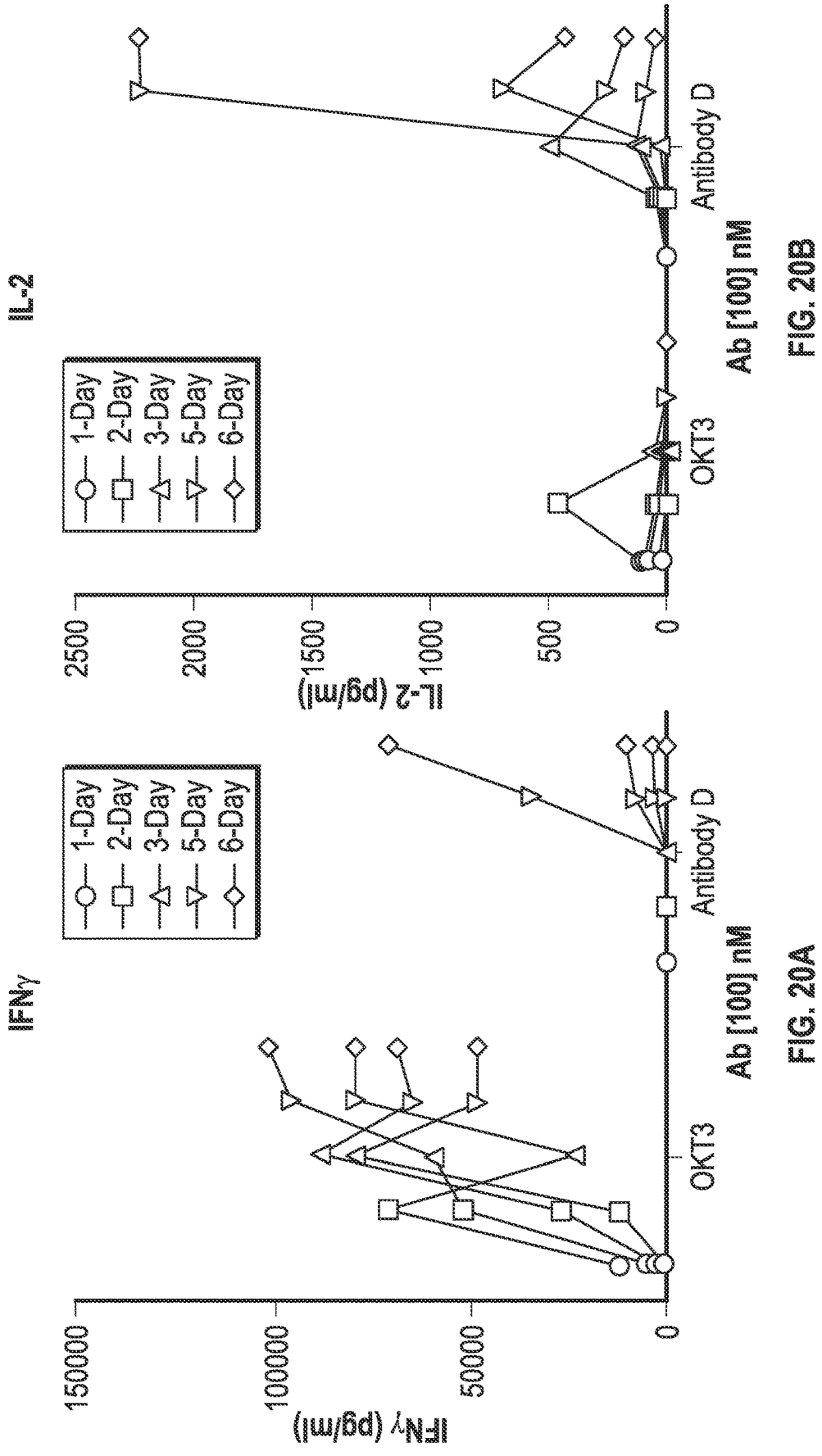


FIG. 20A

FIG. 20B

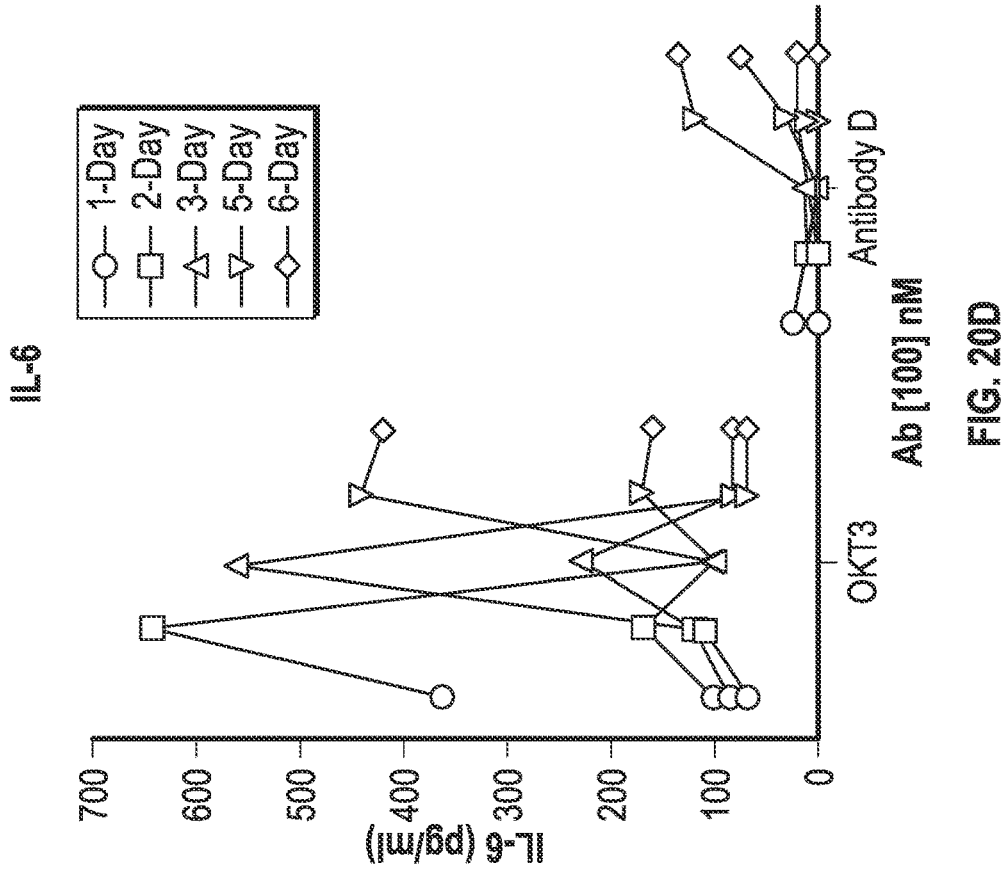


FIG. 20D

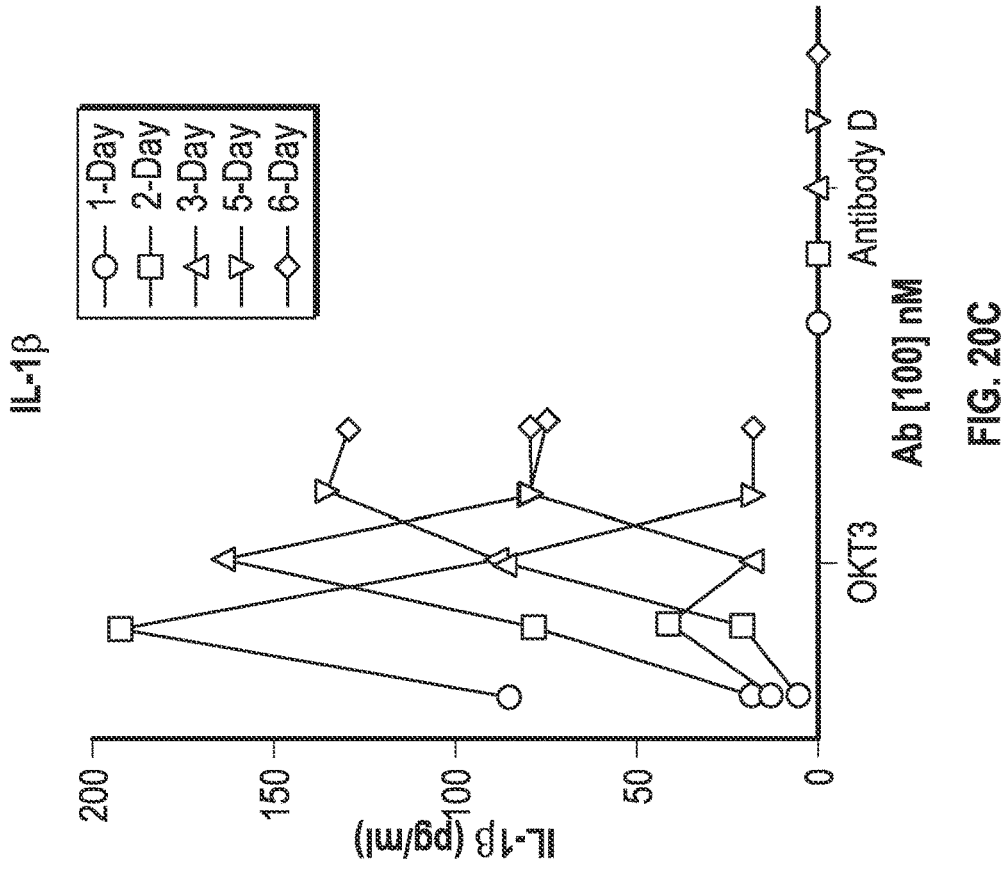


FIG. 20C

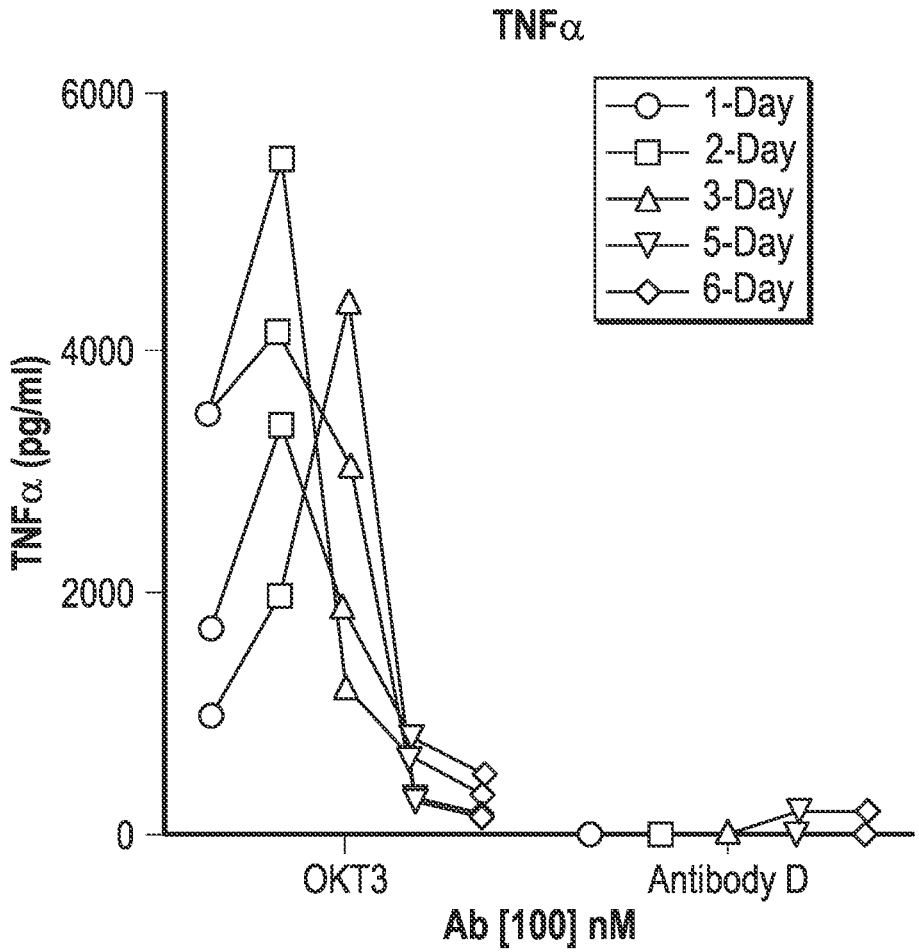

TNFα
6000
4000
2000
0
TNFα (pg/ml)
1-Day
2-Day
3-Day
5-Day
6-Day
OKT3
Antibody D
Ab [100] nM

FIG. 20E

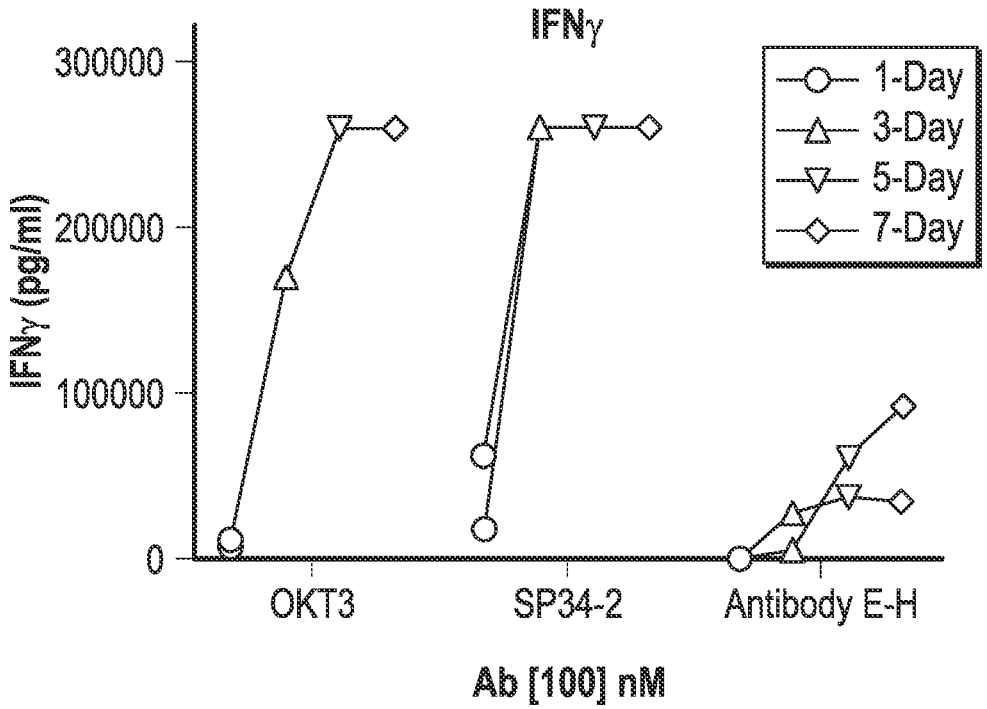


FIG. 21A

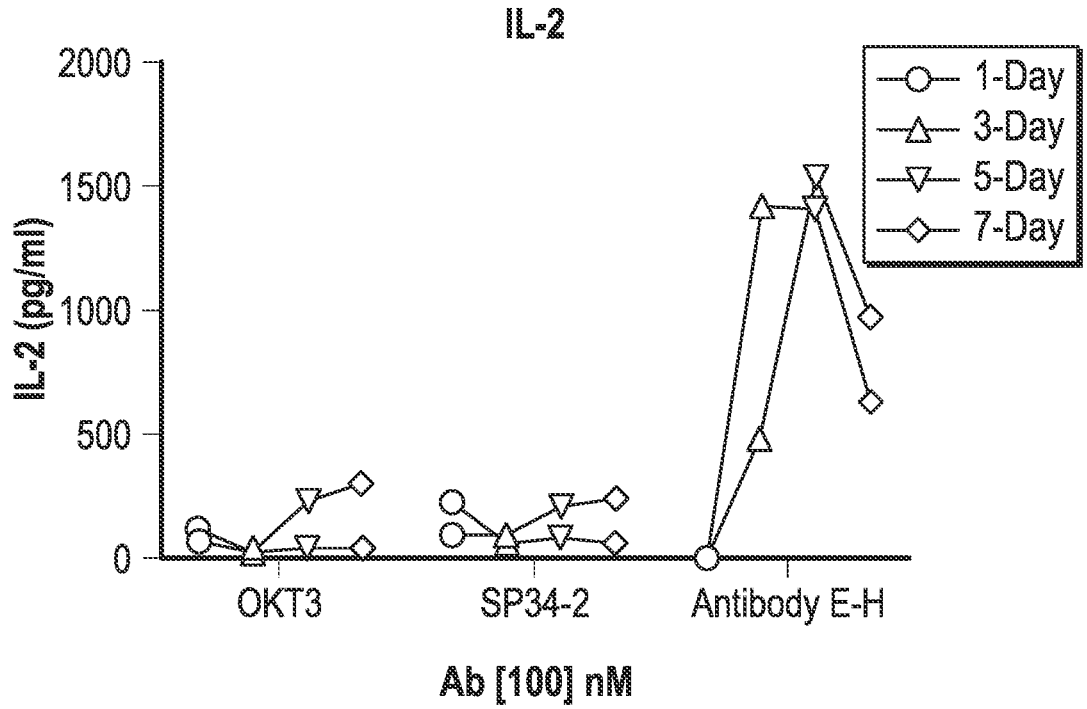


FIG. 21B

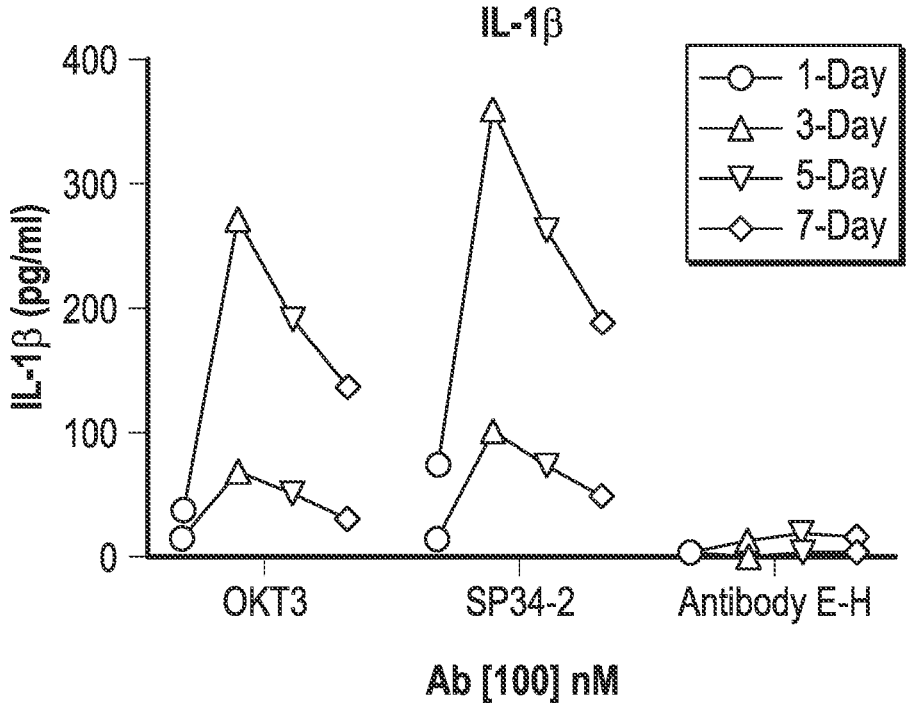


FIG. 22A

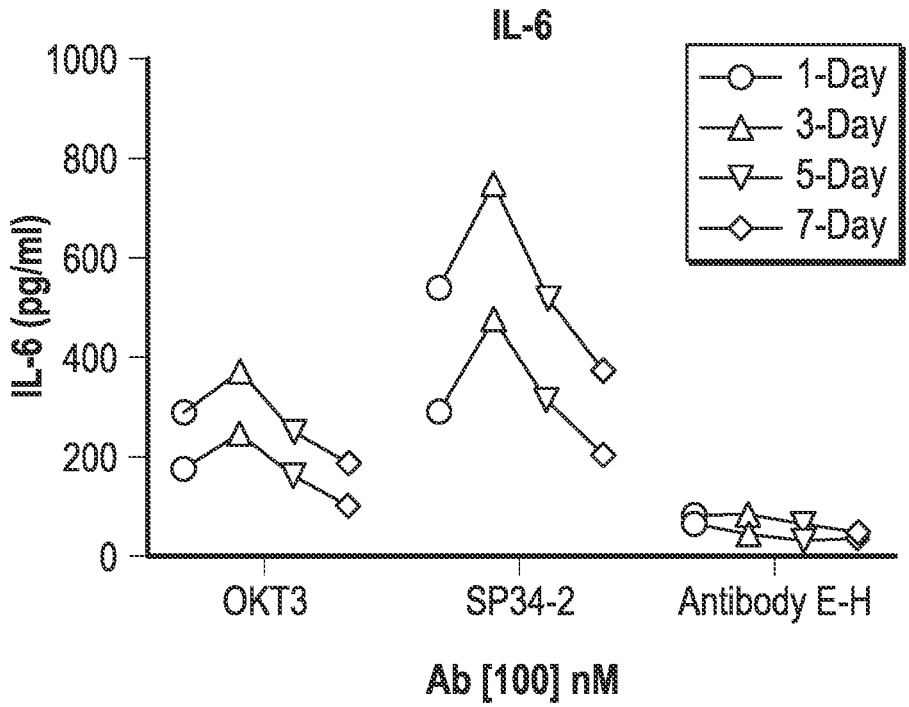


FIG. 22B

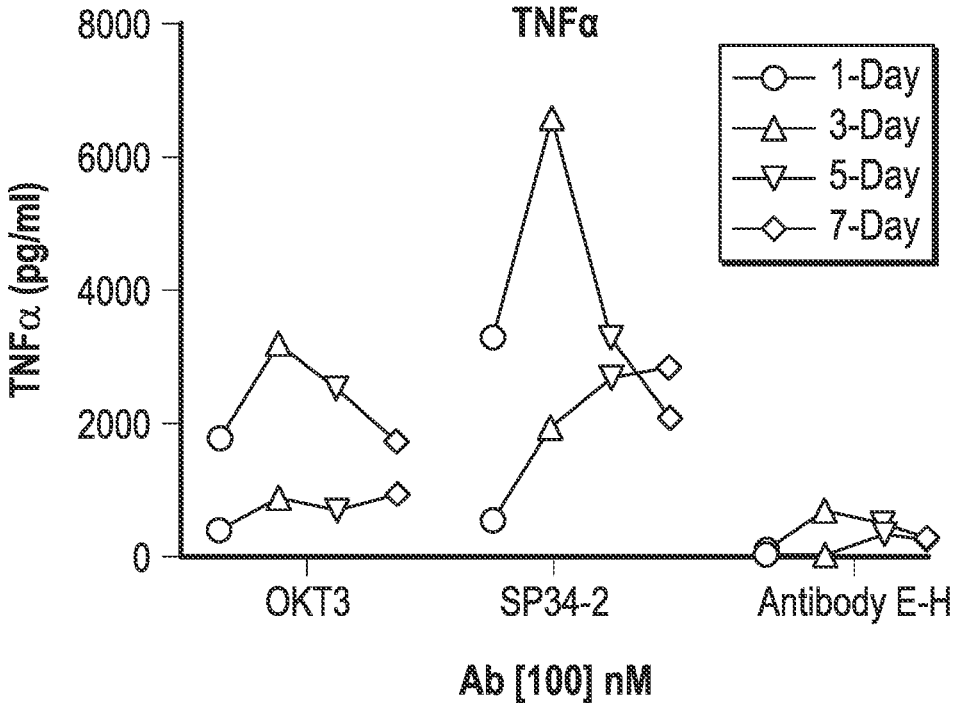


FIG. 22C

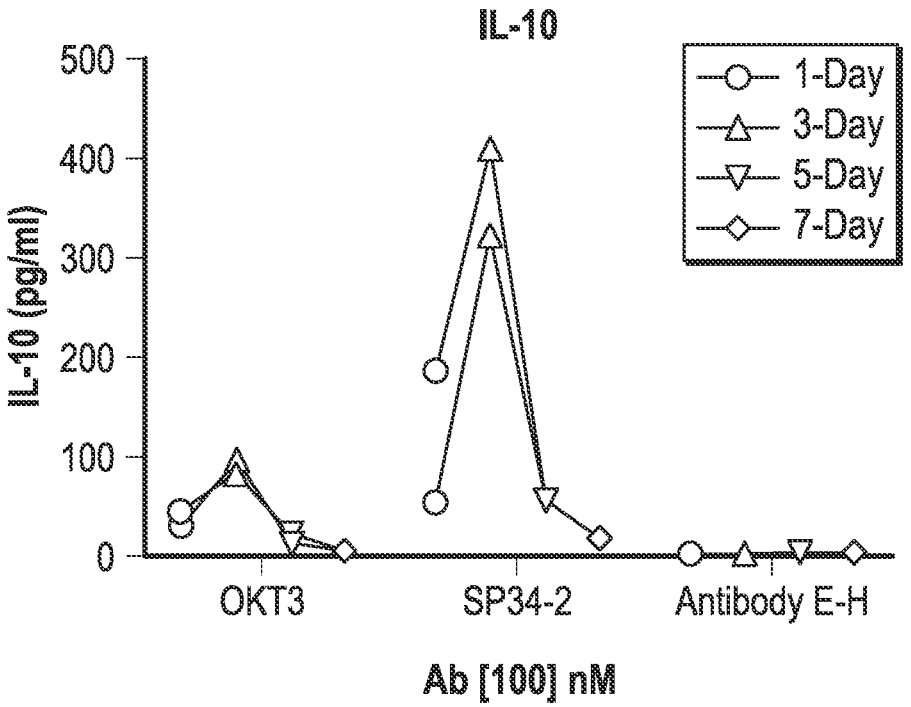


FIG. 22D

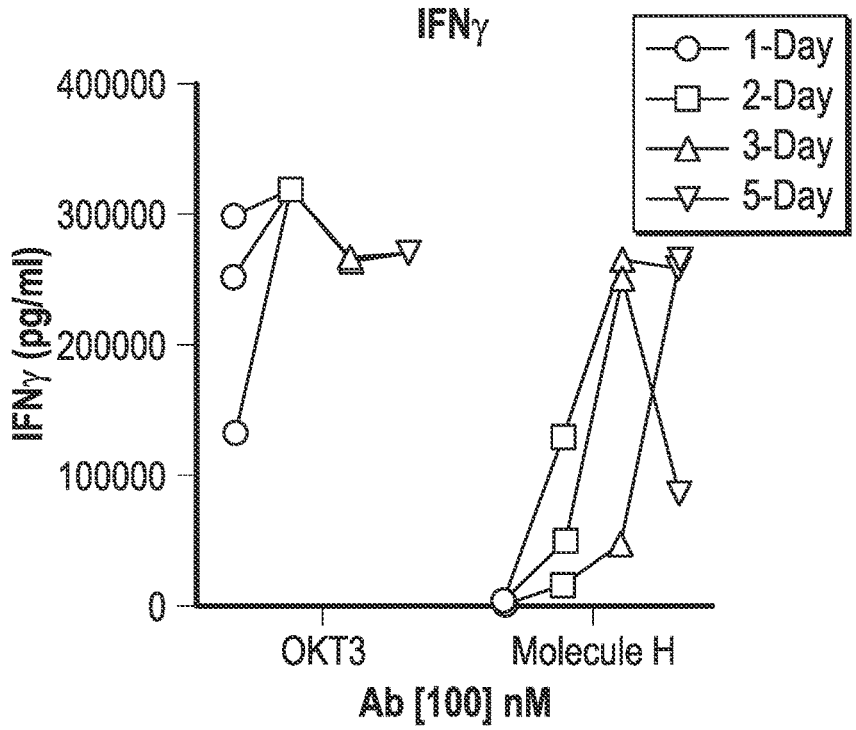


FIG. 23A

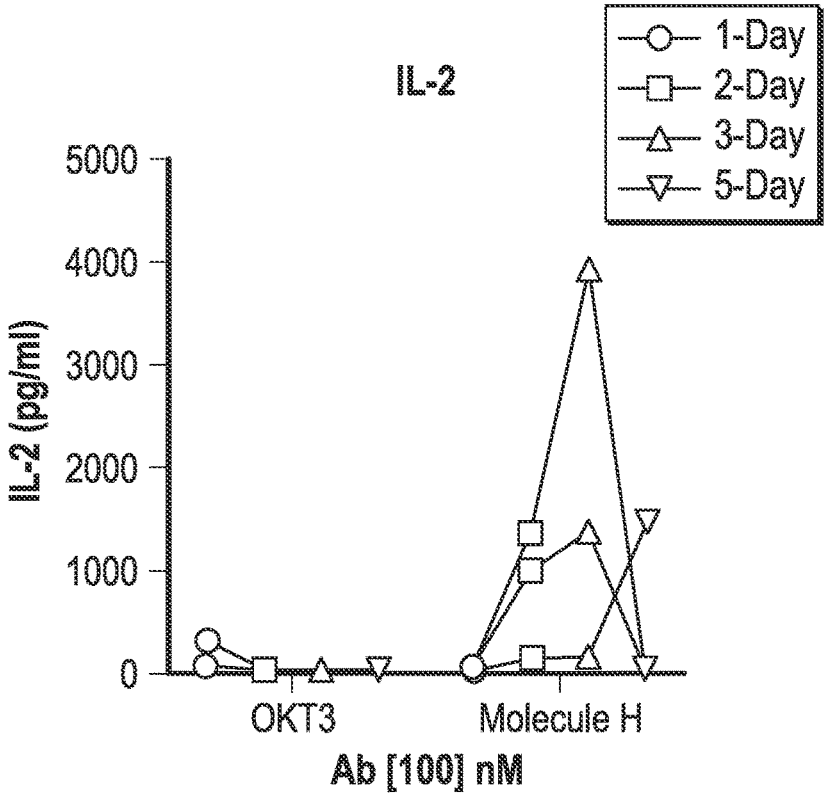


FIG. 23B

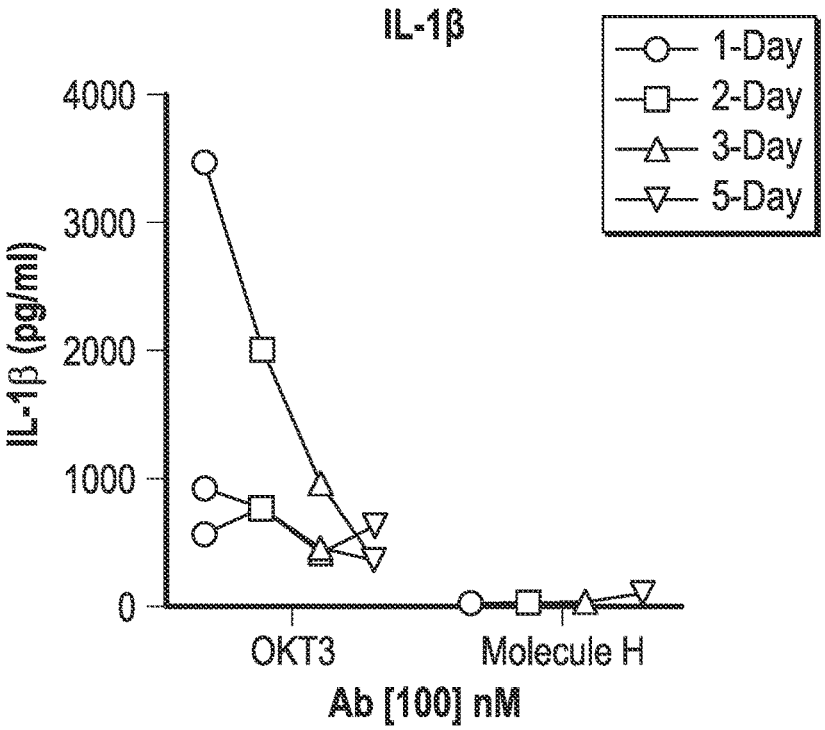


FIG. 23C

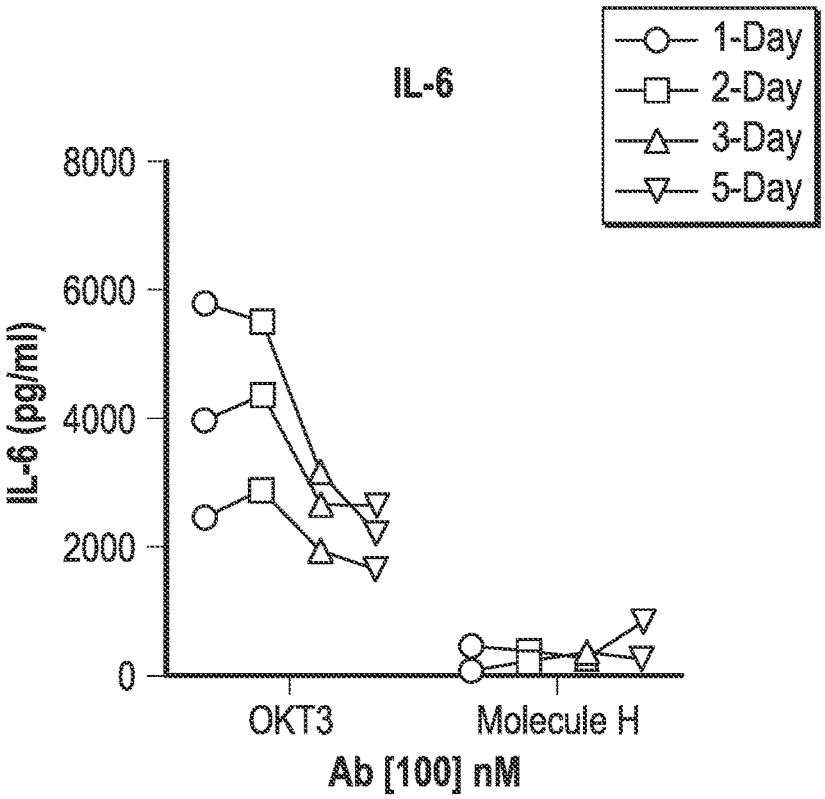


FIG. 23D

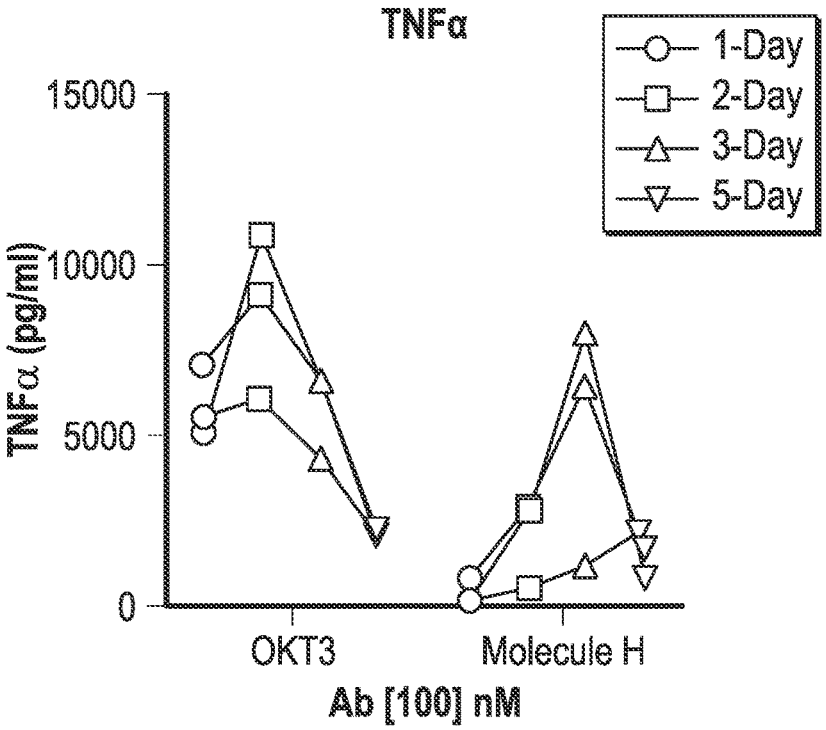


FIG. 23E

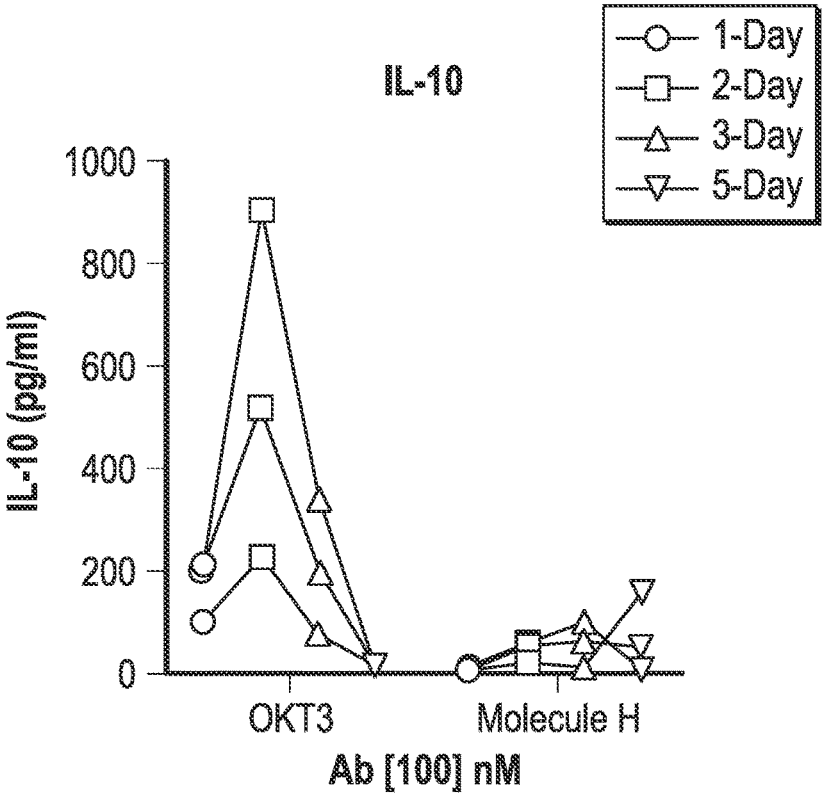


FIG. 23F

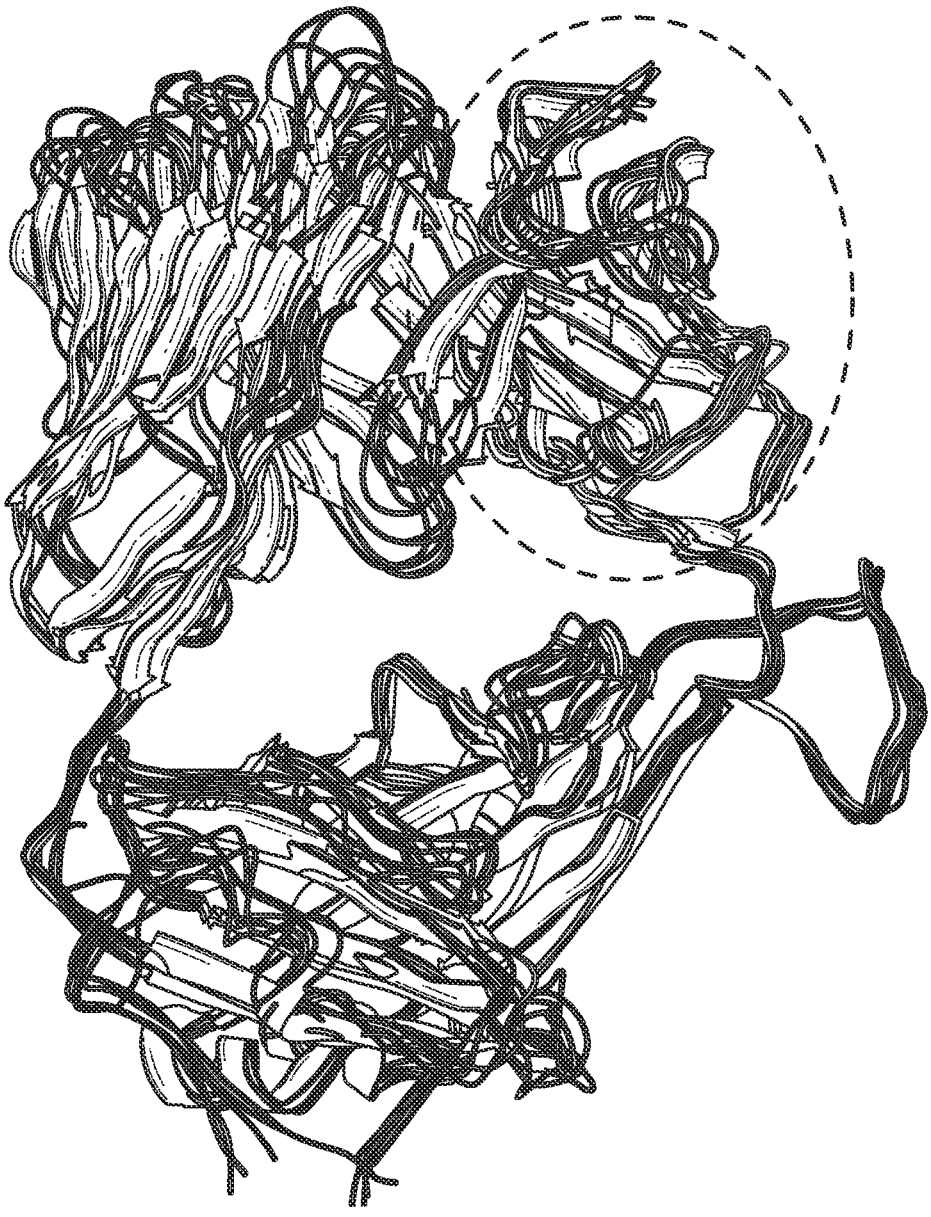


FIG. 24A

6DKP_Vb6_4 -IAGITQAPTSQILAAGRRMTLRCTQ-DMRHNAMYWYRQDLGLGLRLIHYSNTAGTTG--KGEVPDGYSVSRANTDDFPLTLASAVPSQTSVYFCASS-WSFGT--EA
2BNU_Vb6_5 ---GVTQTPKFQVLKTGQSMTLQCAQ-DMNHEYMSWYRQDPGMGLRLIHYSVGAGITD--QGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYFCASS-YVGNTG-EL
4ZDH_Vb28 ---KVTQSSRYLVKRTGEKVFLECVQ-DMDHENMFWYRQDPGLGLRLIYFSYDVKMKE--KGDIPEGYSVSREKKERFSLILASASTDQTSMYLCASS-FLGTGV-EQ
5HHM_Vb19 --GGITQSPKYLFRKEGQNVTLSCEQ-NLNHDAMYWYRQDPGQGLRLIYYSQIVNDFQ--KGDIAEGYSVSREKKESFPLTVTSAQKNPTAFYLCASS--SRSSY-EQ
5KSA_Vb9 ---GVTQTPKHLITATGQRVTLRCSP-RSGDLSVYWYQQSLDQGLQFLIQYYNGEERA--KGNILERFSAQQFPDLHSELNLSSLELGDSALYFCASS-VAGTPSYEQ
5BS0_Vb5_1 --AGVTQTPRYLIKTRGQQVTLSCSP-ISGHRSVSWYQQTPGQGLQFLFEYFSETQRN--KGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYLCASS-FNMAIG--Q
3MFG_Vb20_1--AVVSQHPSRVIVKSGTSVKIECRSLDFQATTMFWYRQFPK-,SLMLMATSNEGSKATYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSGFYICSA-----LAQDTQ
5C0C_Vb12_4MDAGVIQSPRHEVTEMGQQVTLRCKPIS-GHDYLFWYRQTMMRGLELLIYFNNNVPID-DSGMPEDRFSAKMPNASFSTLKIQPSEPRDSAVYFCASSLWEKLAKNIQ

FIG. 24B

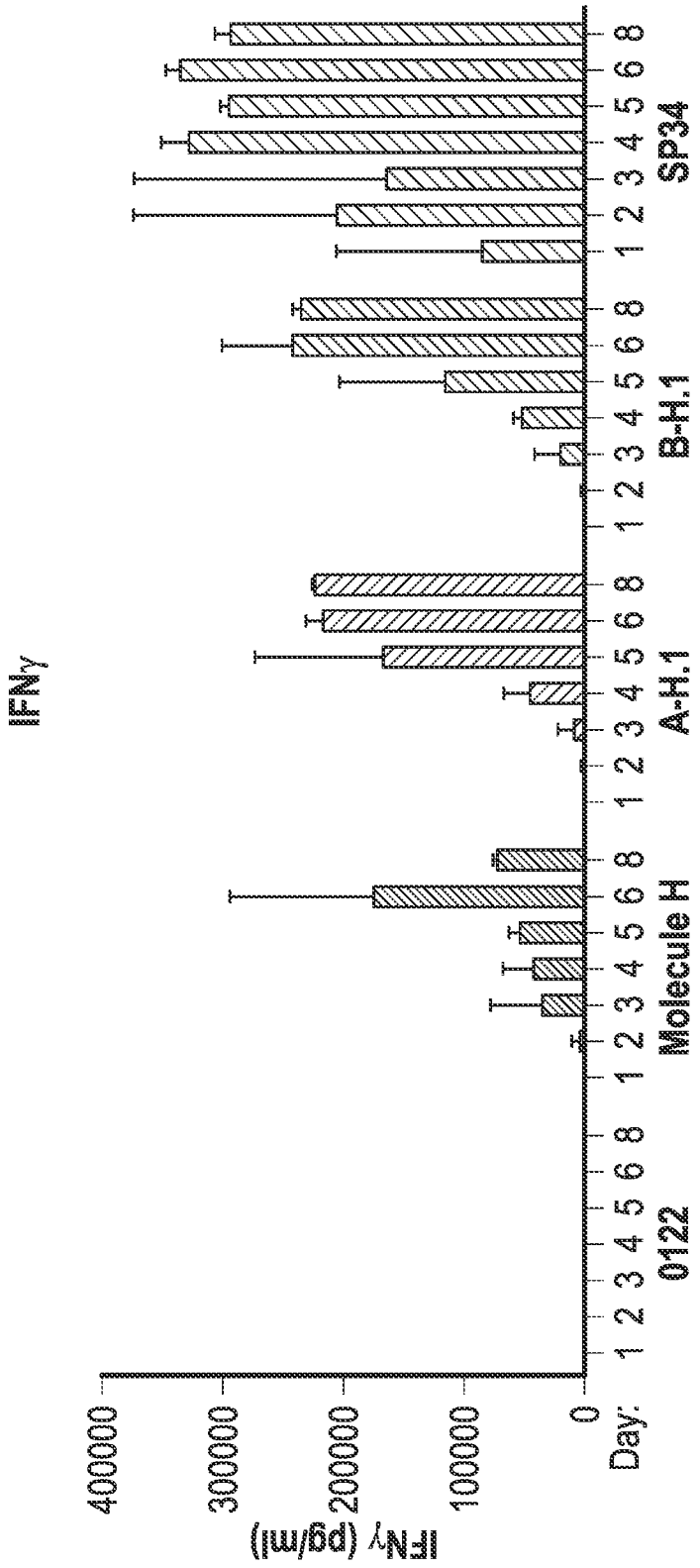

IFNγ
IFNγ (pg/ml)
400000
300000
200000
100000
0
Day:
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM
1 2 3 4 5 6 8

FIG. 25A

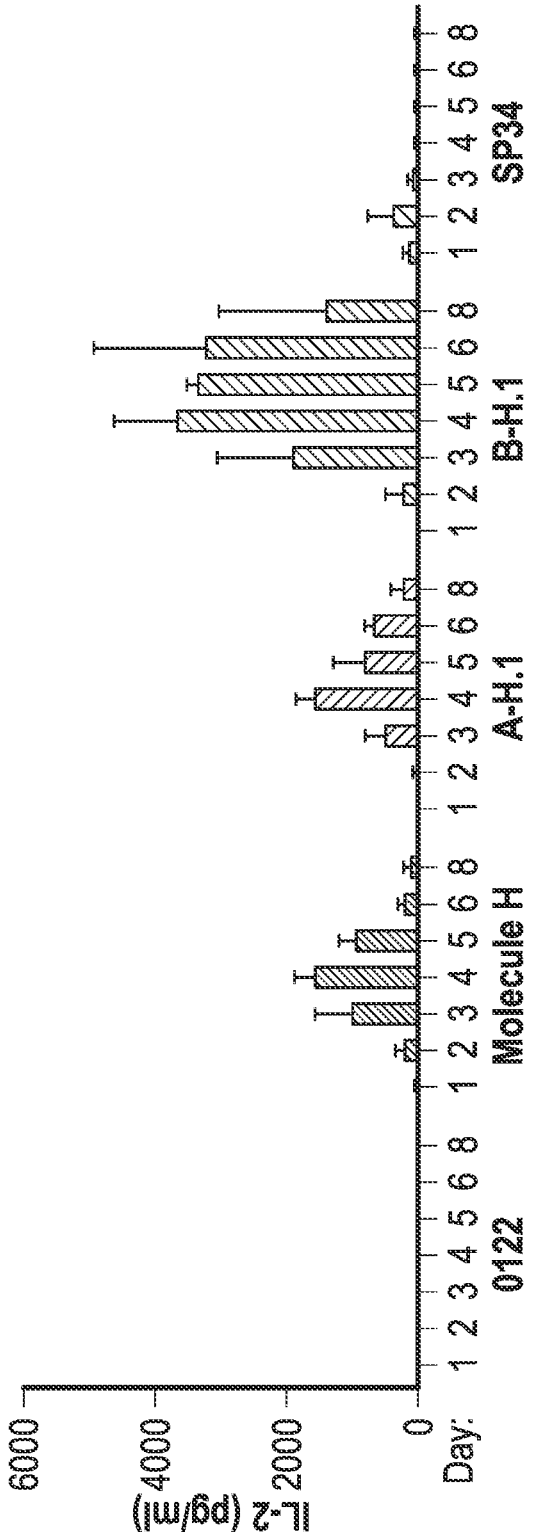

IL-2
IL-2 (pg/ml)
6000
4000
2000
0
Day:
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25B

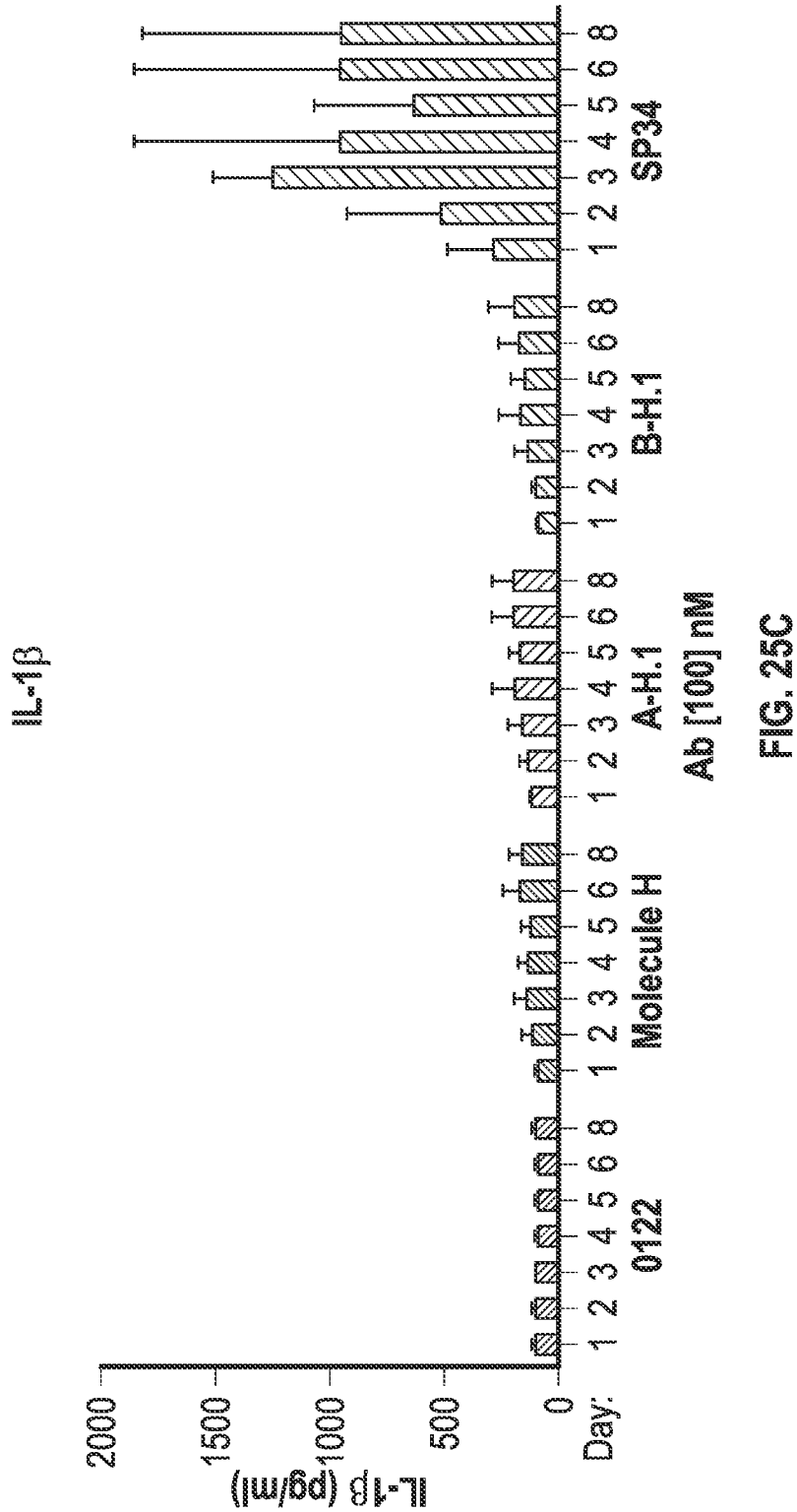

IL-1β
IL-1β (pg/ml)
2000
1500
1000
500
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25C

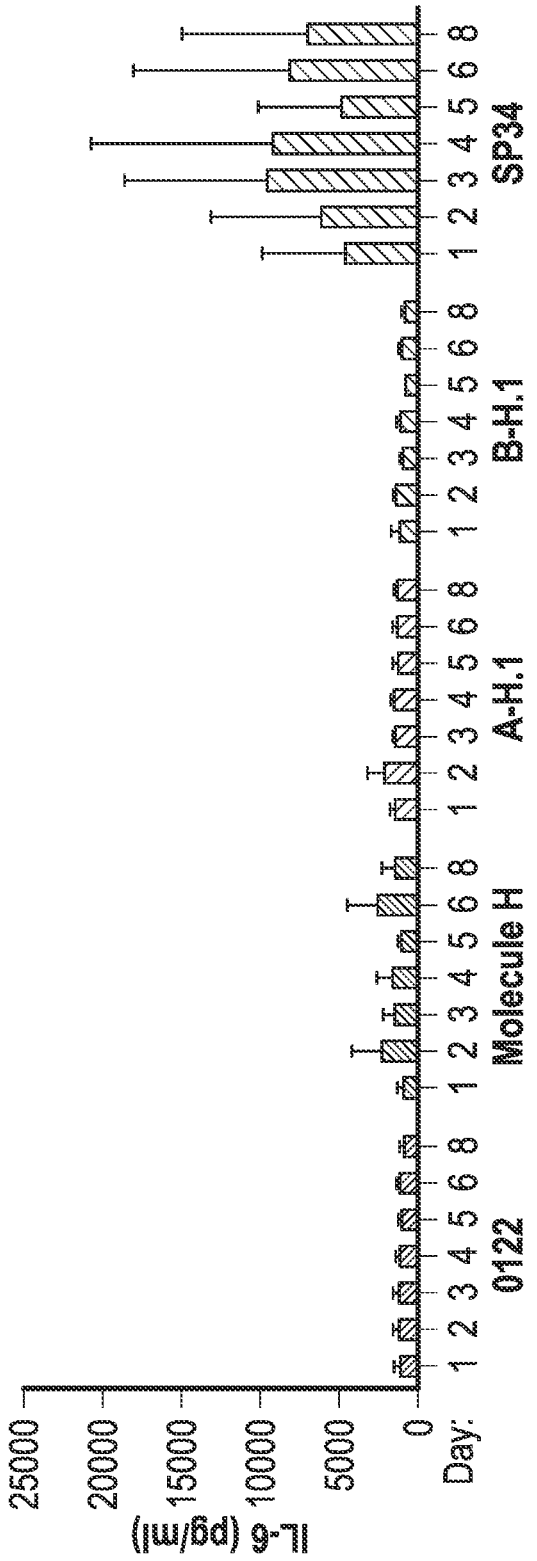

IL-6
IL-6 (pg/ml)
25000
20000
15000
10000
5000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25D

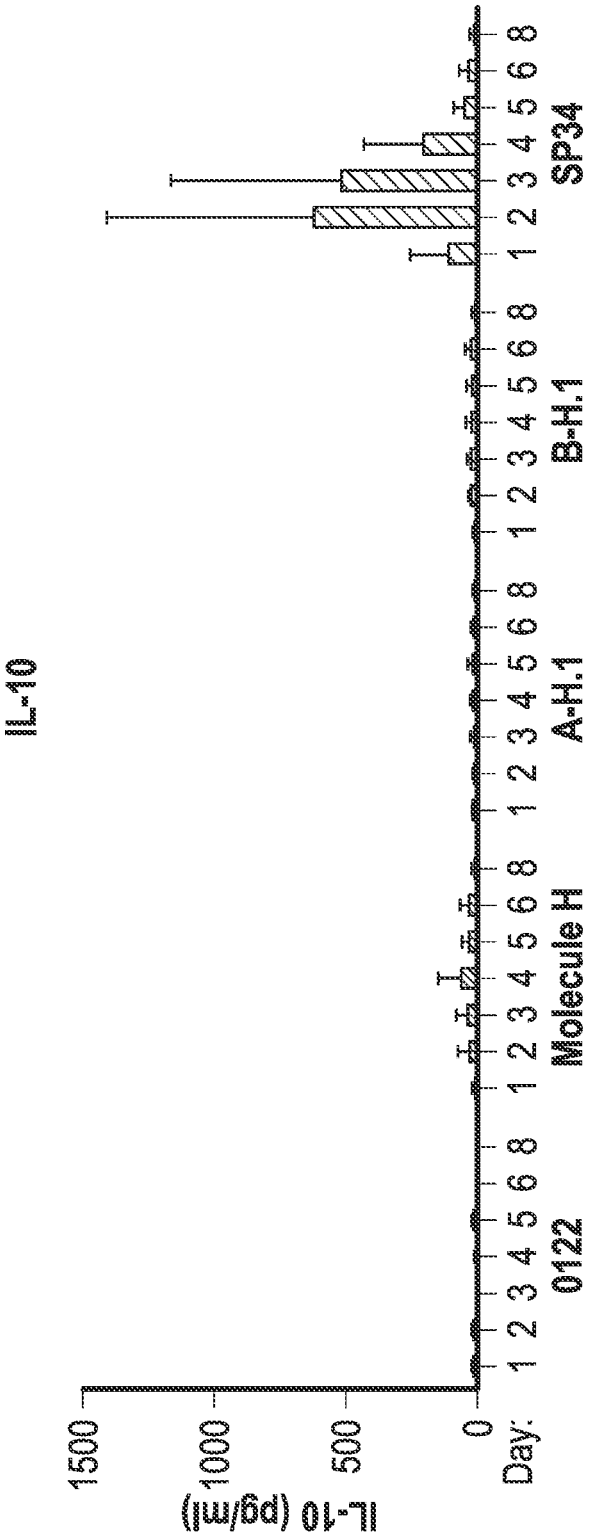

IL-10
IL-10 (pg/ml)
1500
1000
500
0
Day:
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25E

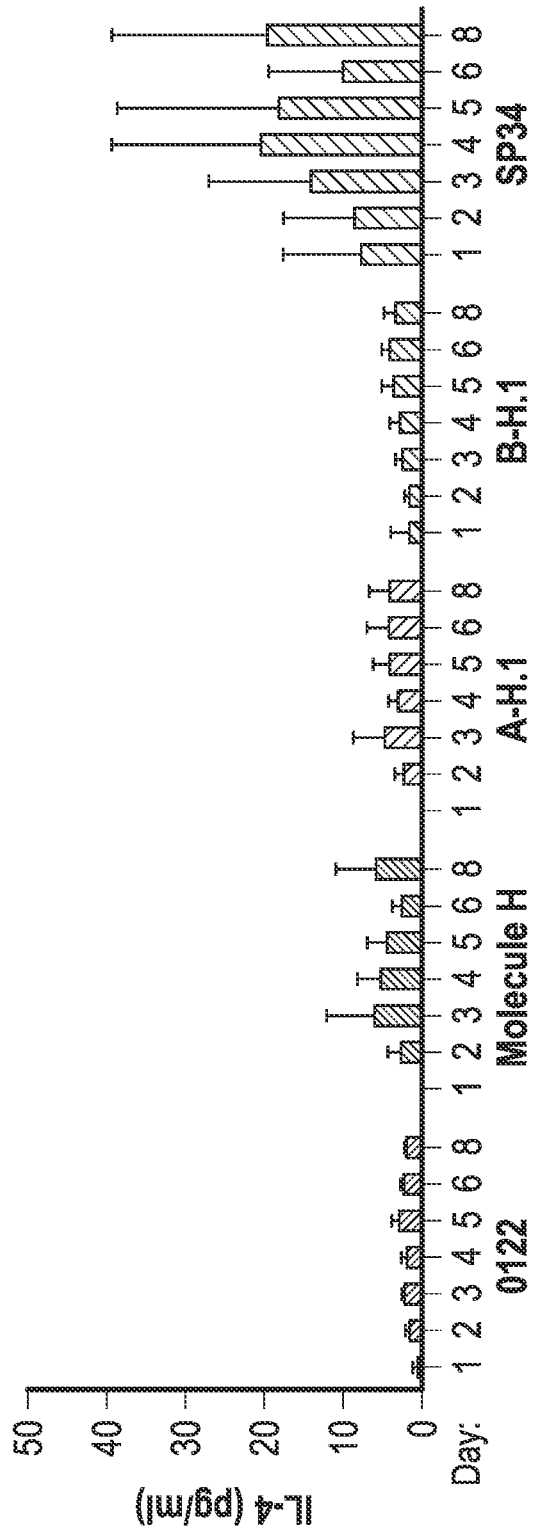

IL-4
IL-4 (pg/ml)
50
40
30
20
10
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25F

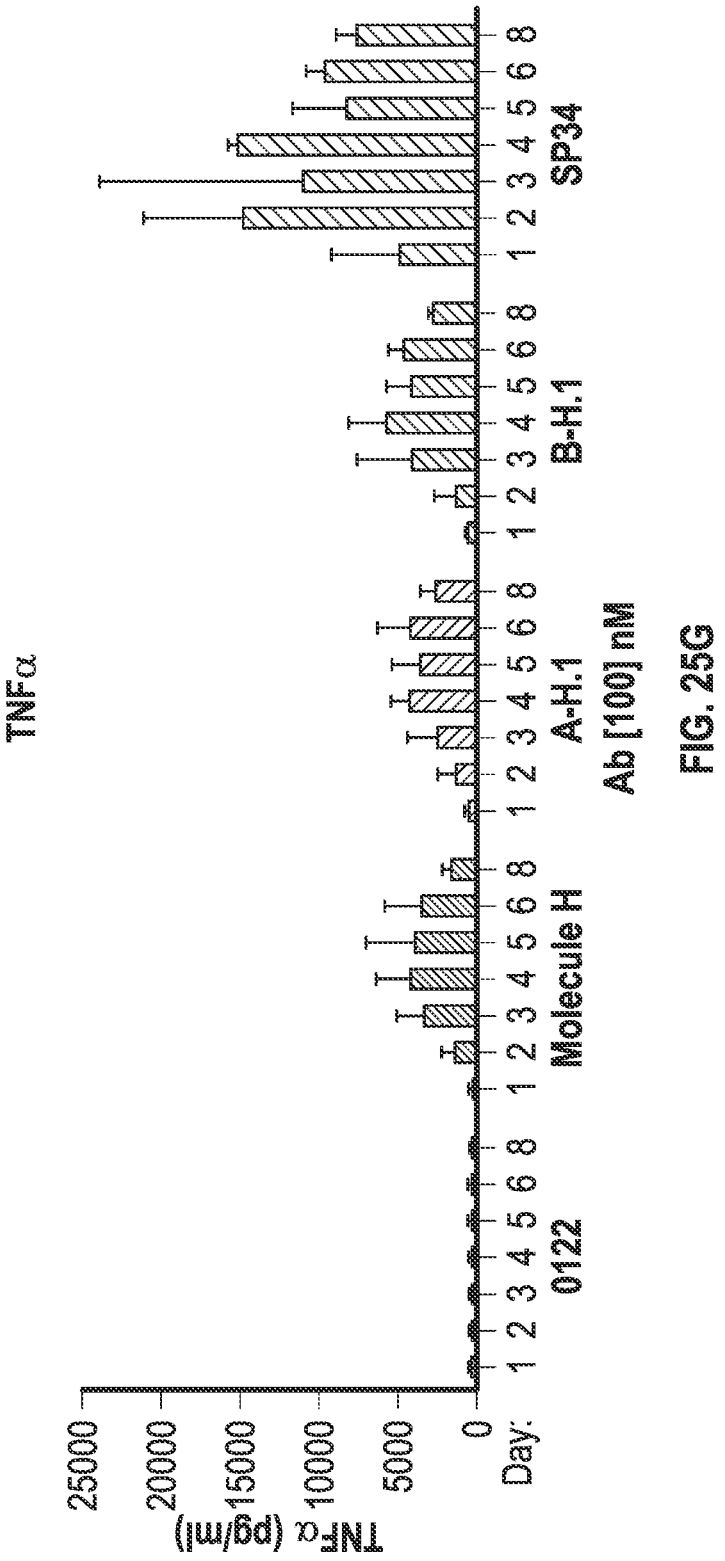

TNFα
TNFα (pg/ml)
25000
20000
15000
10000
5000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25G

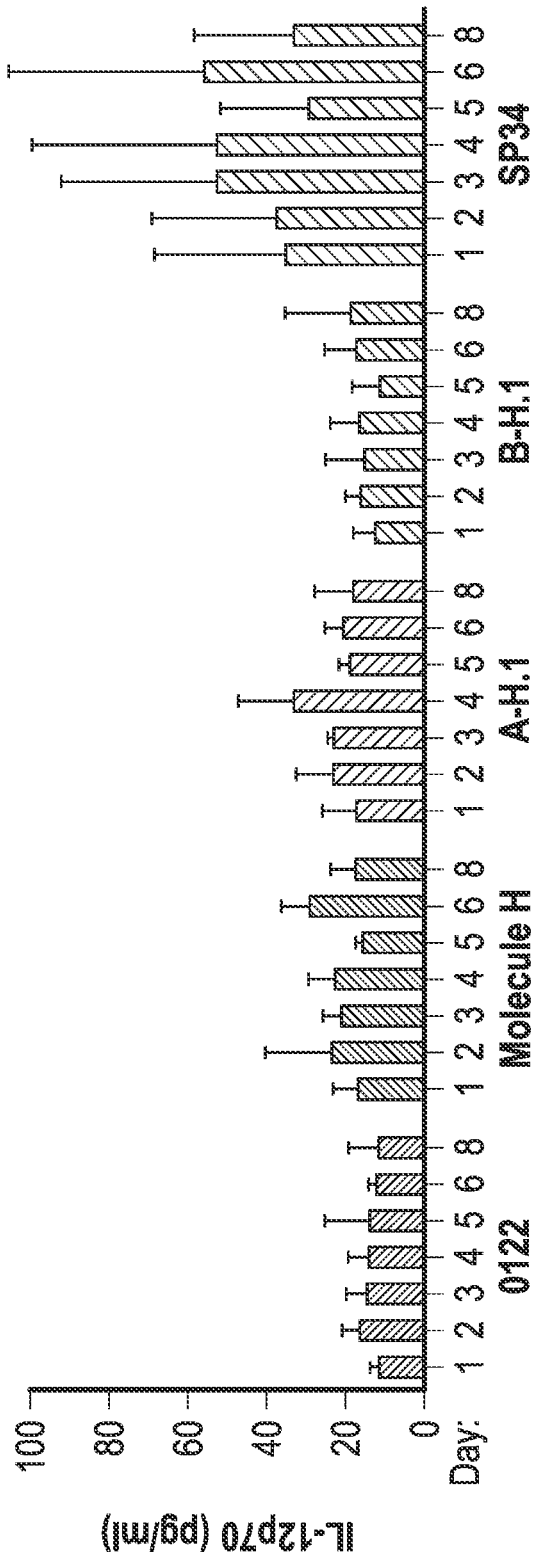

IL-12p70
IL-12p70 (pg/ml)
100
80
60
40
20
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25H

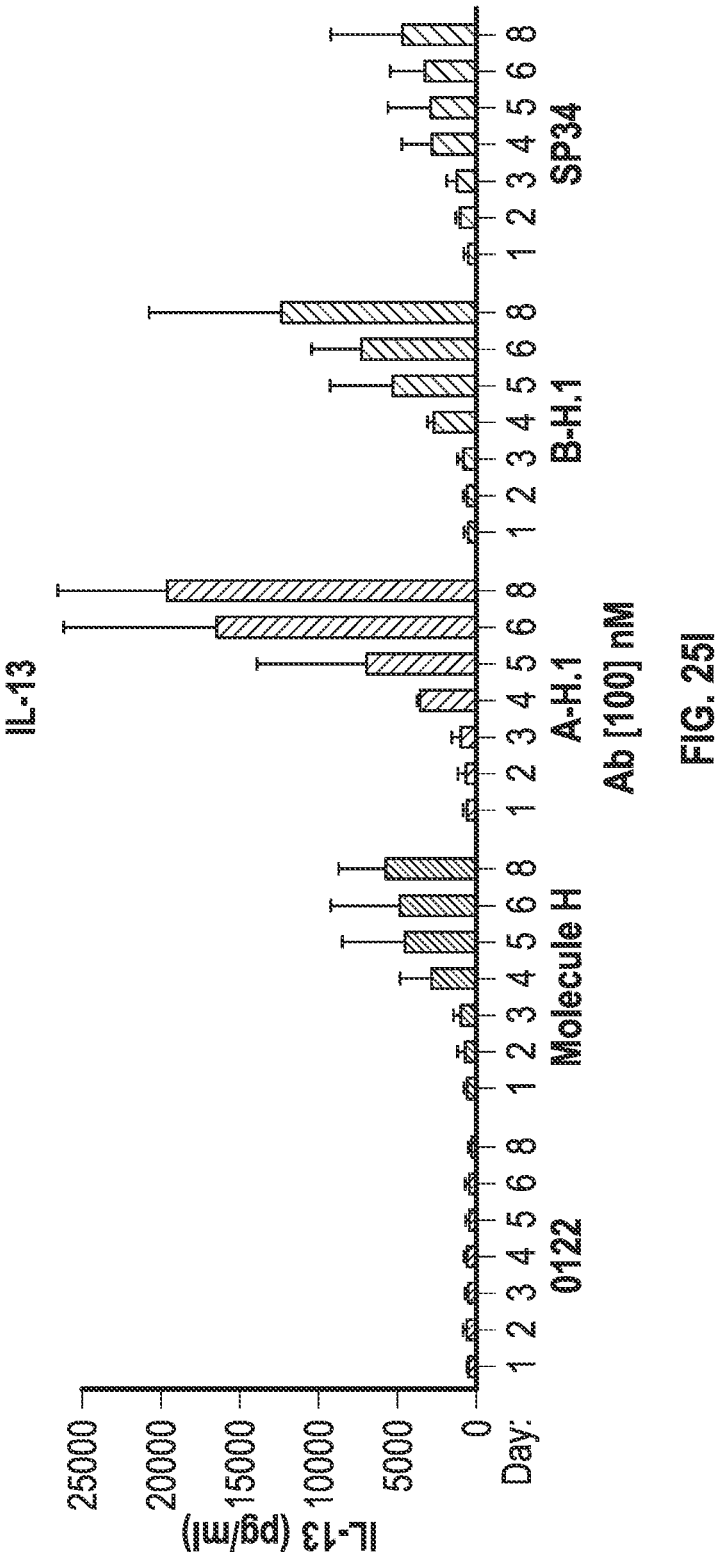

IL-13
IL-13 (pg/ml)
25000
20000
15000
10000
5000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25I

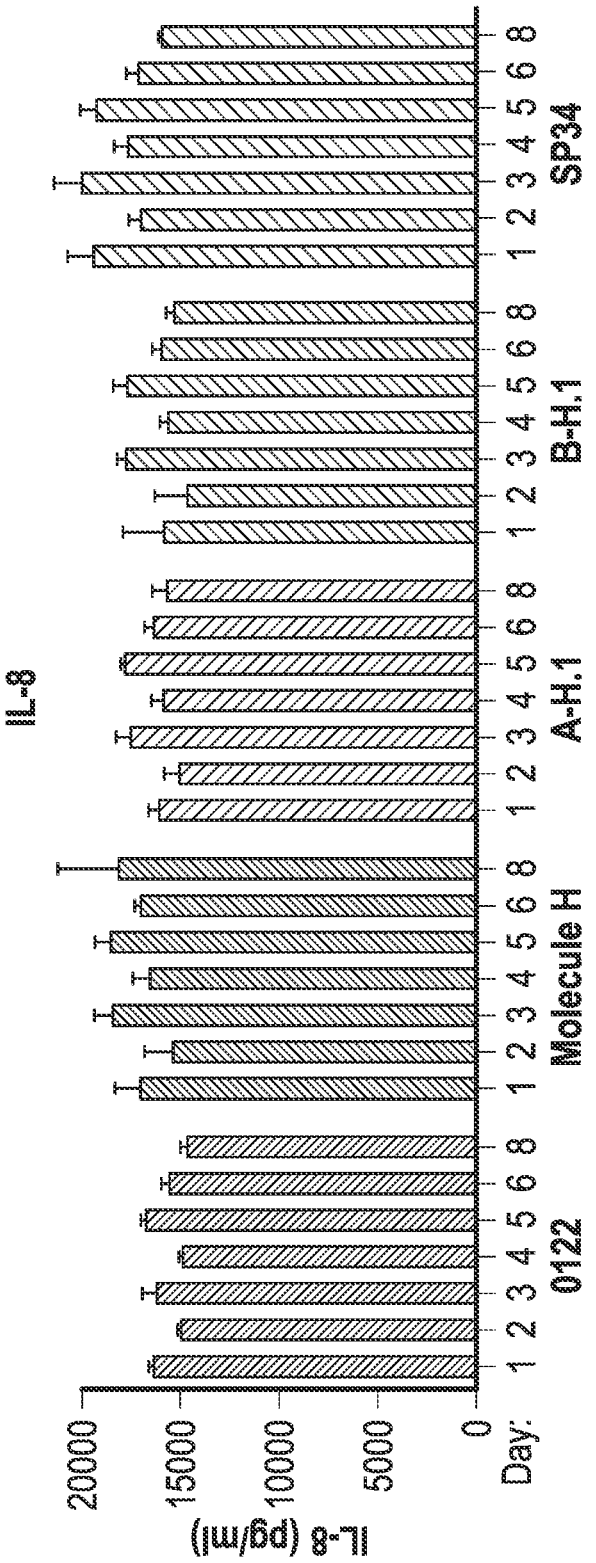

IL-8
IL-8 (pg/ml)
20000
15000
10000
5000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 25J

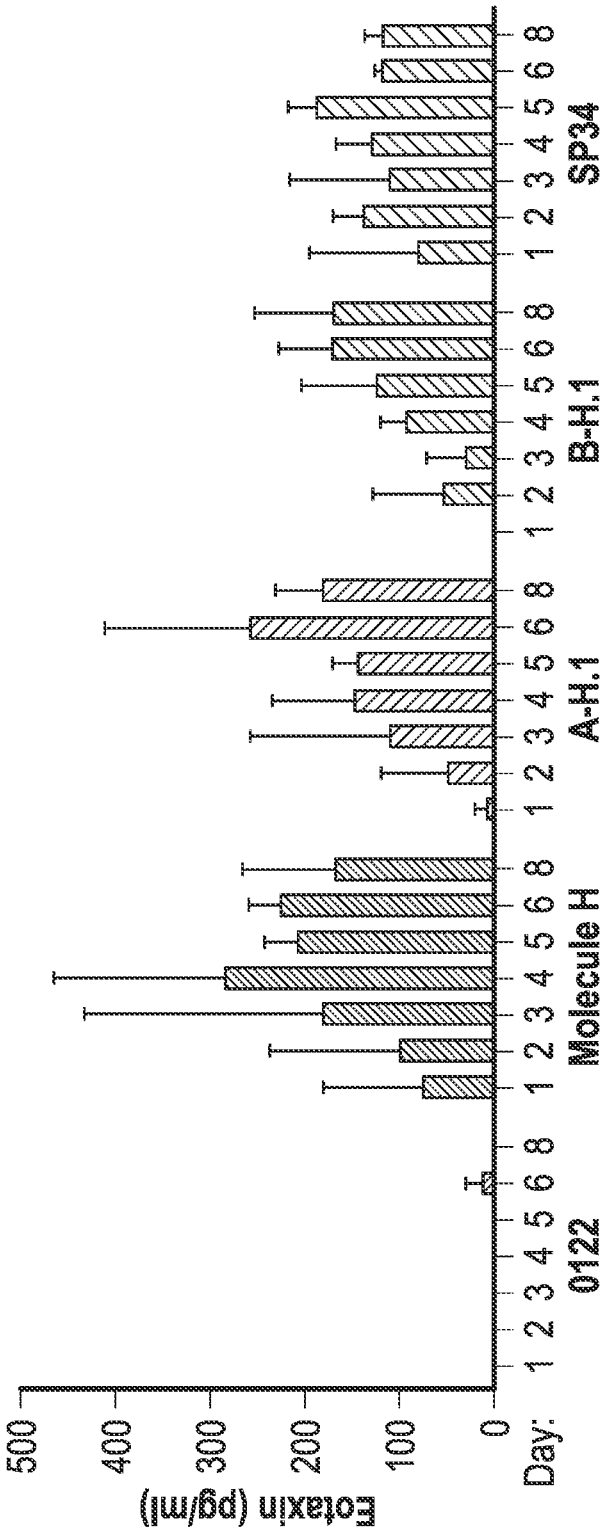

Eotaxin
Eotaxin (pg/ml)
500
400
300
200
100
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100] nM

FIG. 26A

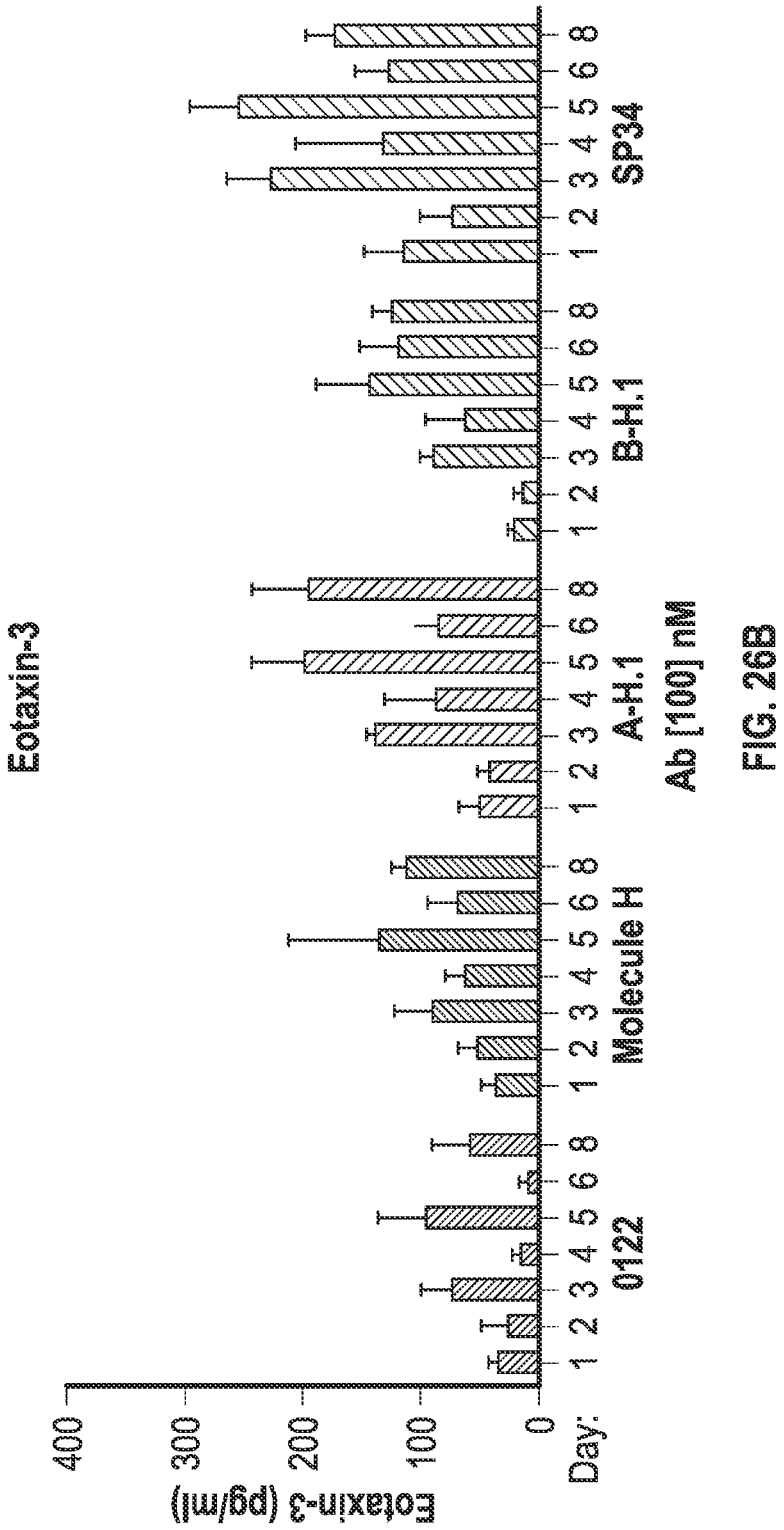

Eotaxin-3
Eotaxin-3 (pg/ml)
400
300
200
100
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 26B

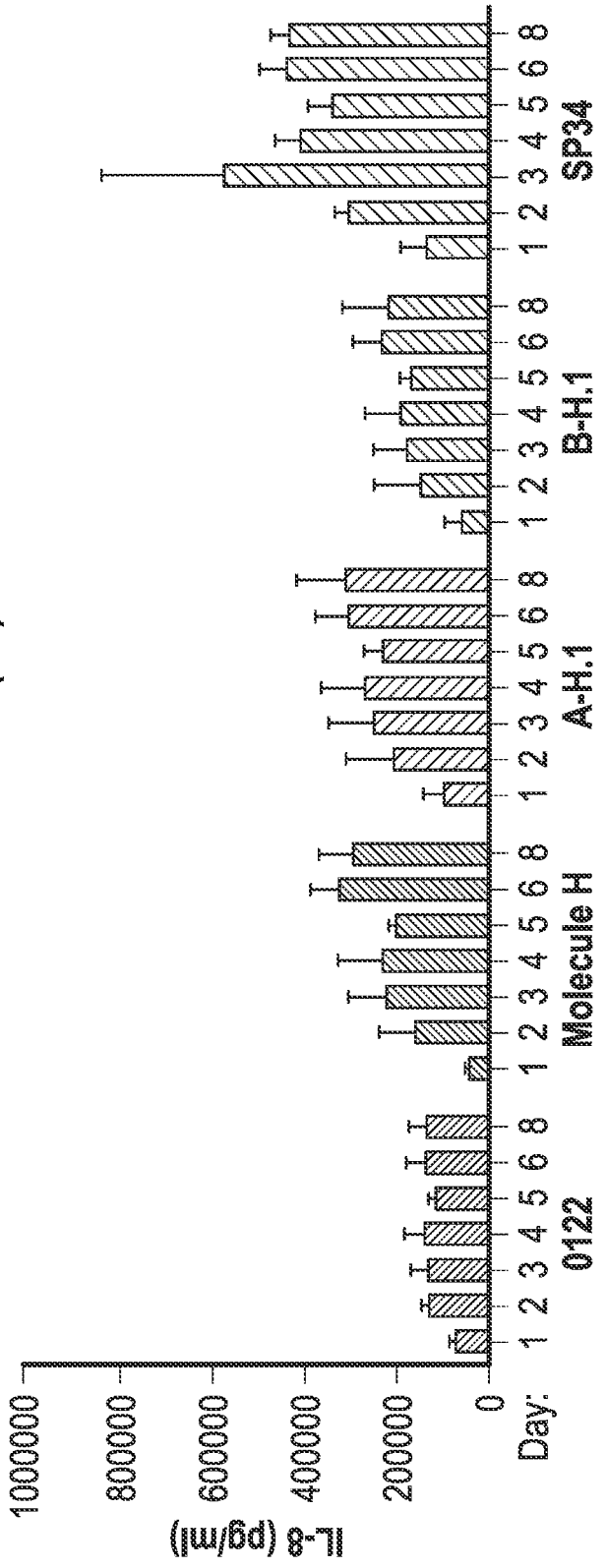

IL-8 (HA)
IL-8 (pg/ml)
1000000
800000
600000
400000
200000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 26C

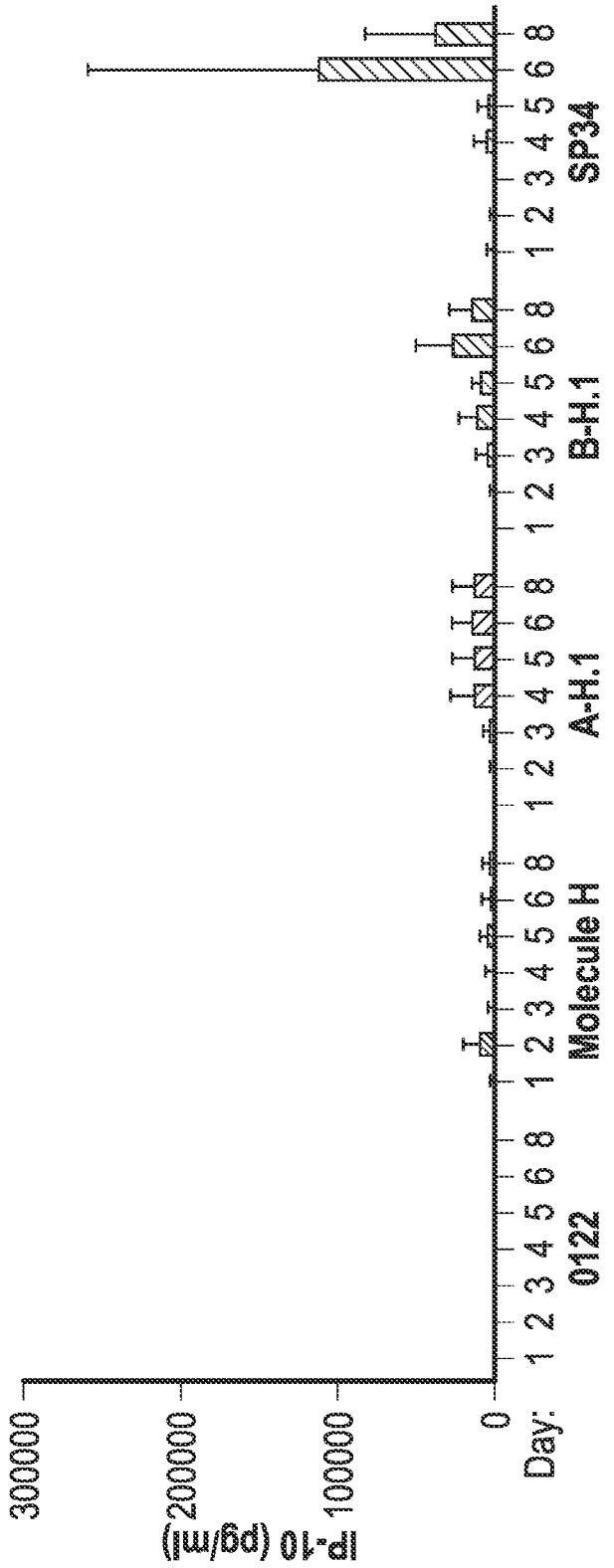

IP-10
IP-10 (pg/ml)
300000
200000
100000
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100] nM

FIG. 26D

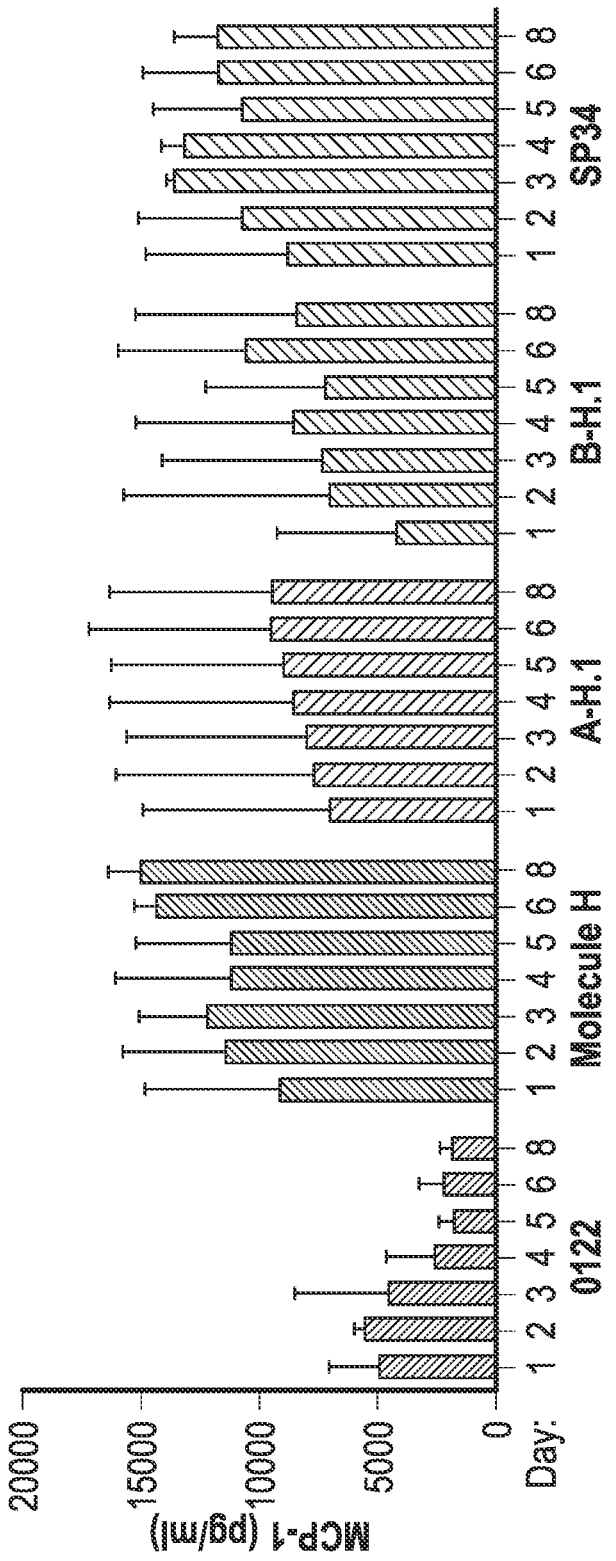

MCP-1
MCP-1 (pg/ml)
20000
15000
10000
5000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100] nM

FIG. 26E

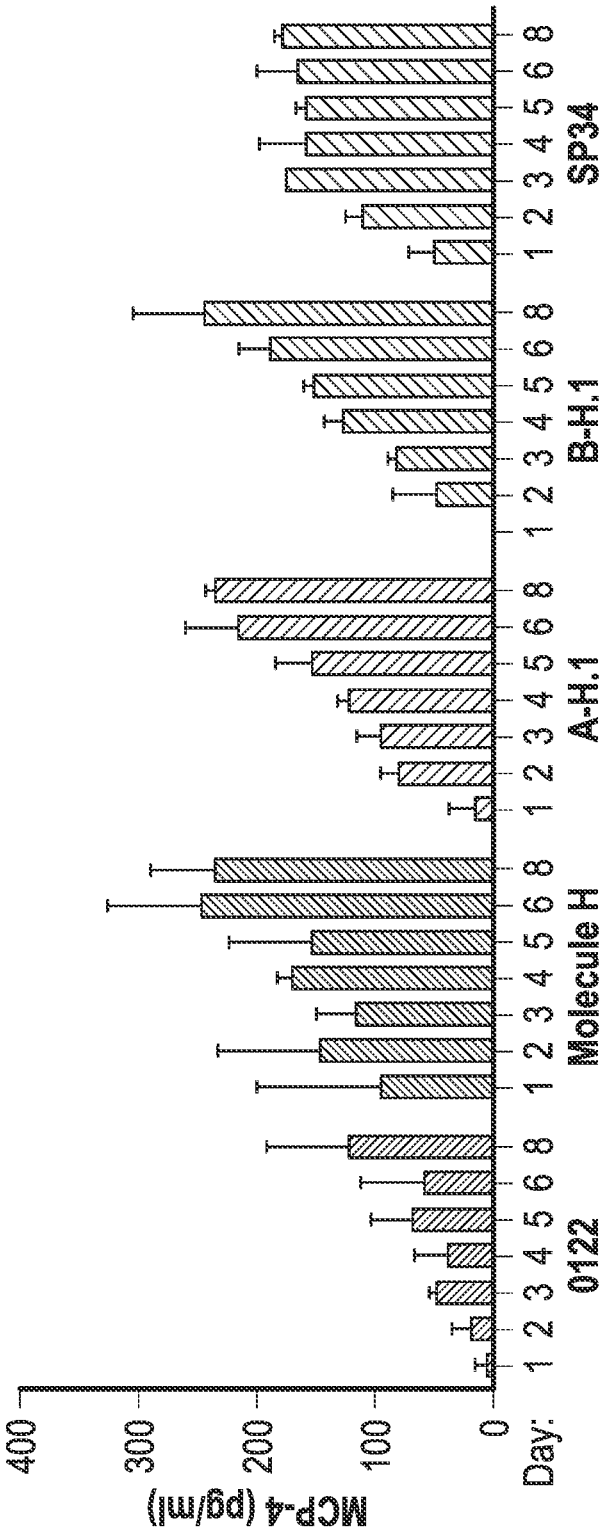

MCP-4
MCP-4 (pg/ml)
400
300
200
100
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100] nM

FIG. 26F

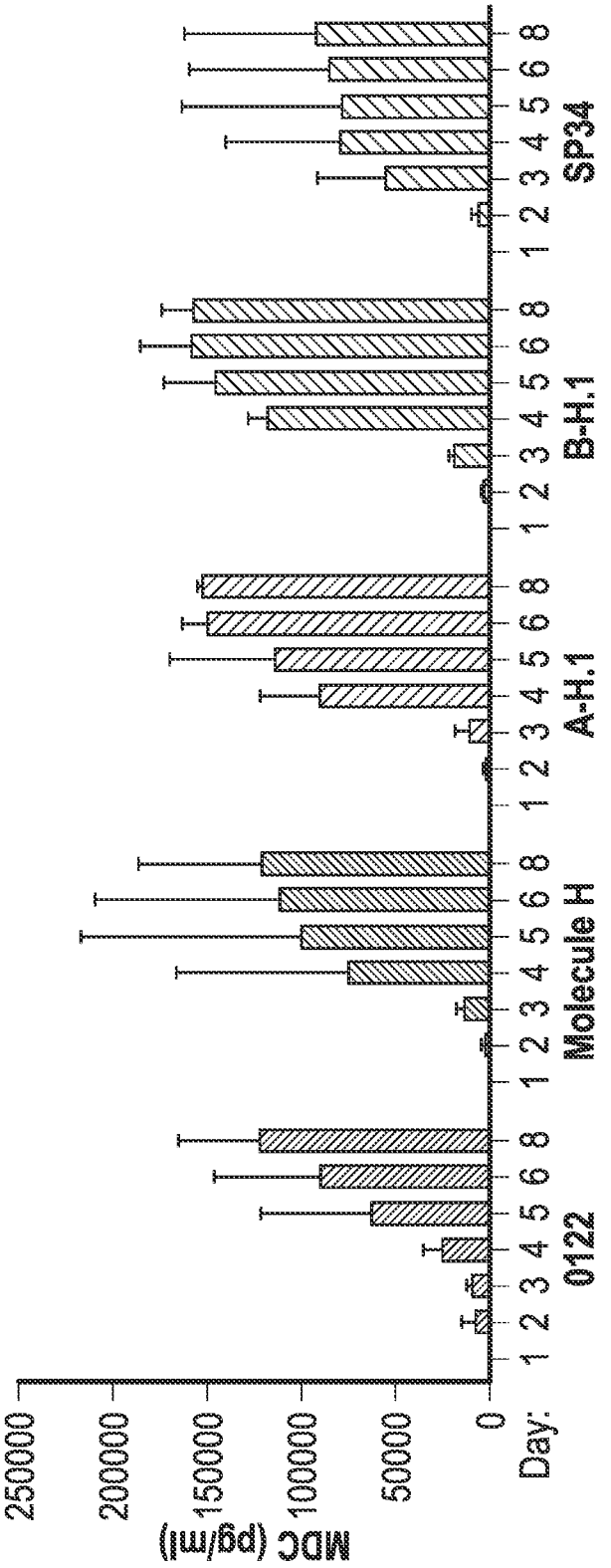

MDC
MDC (pg/ml)
250000
200000
150000
100000
50000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100] nM

FIG. 26G

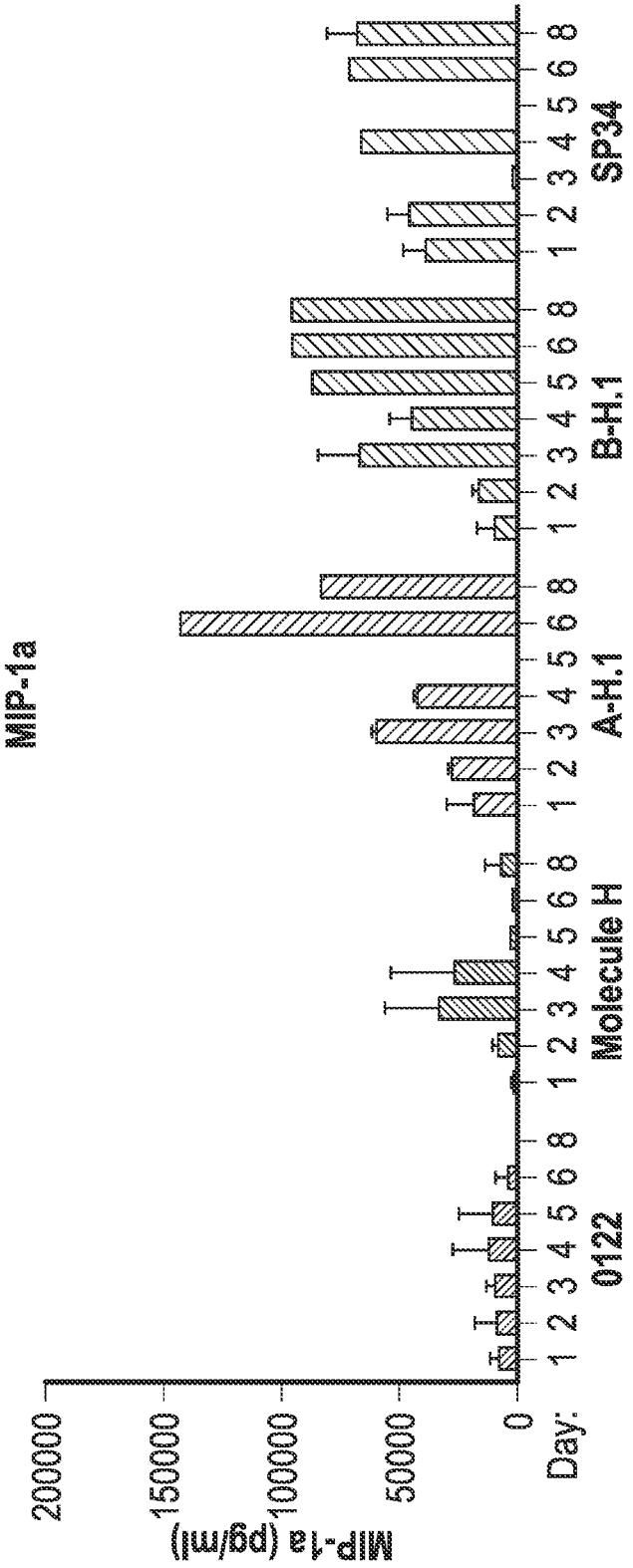

MIP-1a
MIP-1a (pg/ml)
200000
150000
100000
50000
0
Day:
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
1 2 3 4 5 6 8
Ab [100] nM

FIG. 26H

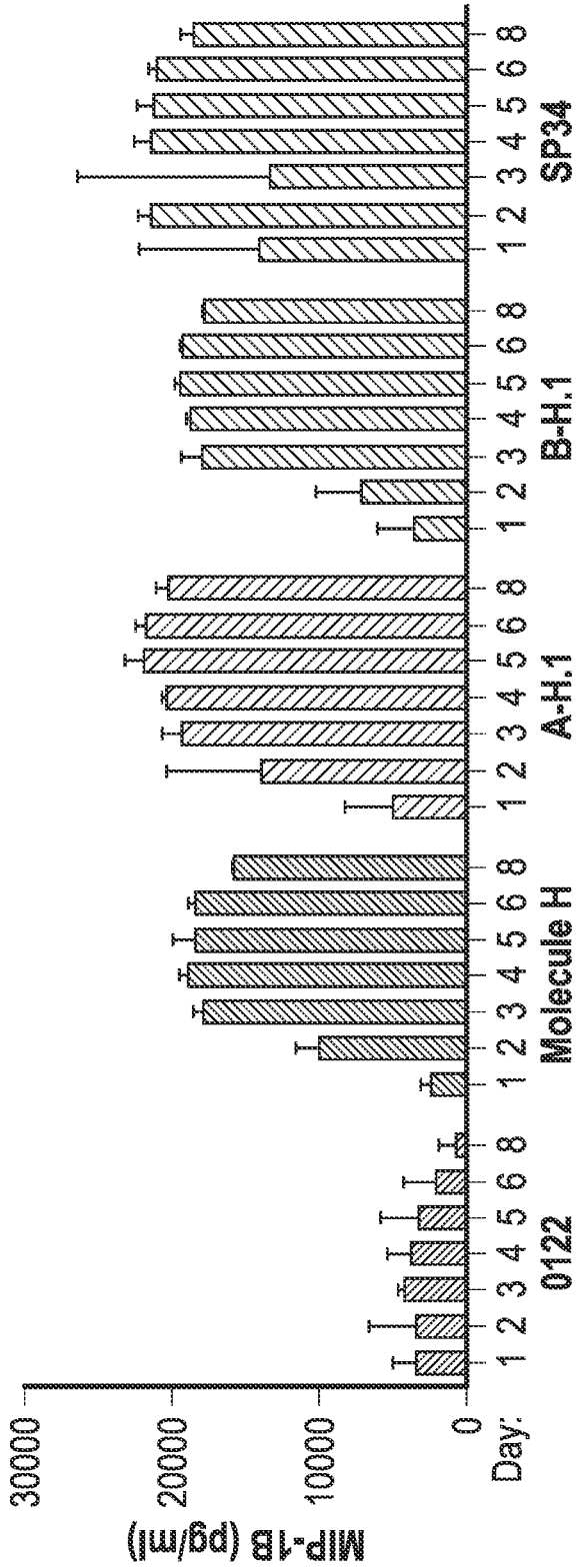

MIP-1B
MIP-1B (pg/ml)
30000
20000
10000
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27A

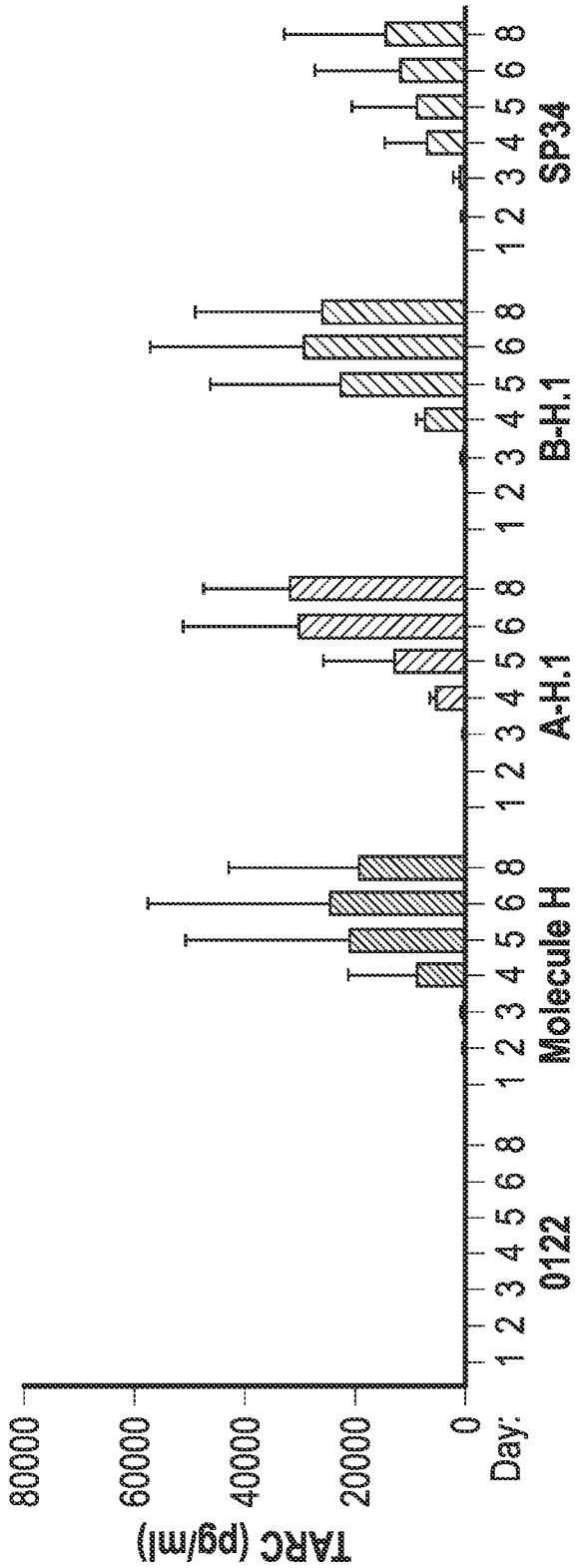

TARC
TARC (pg/ml)
80000
60000
40000
20000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100]nM

FIG. 27B

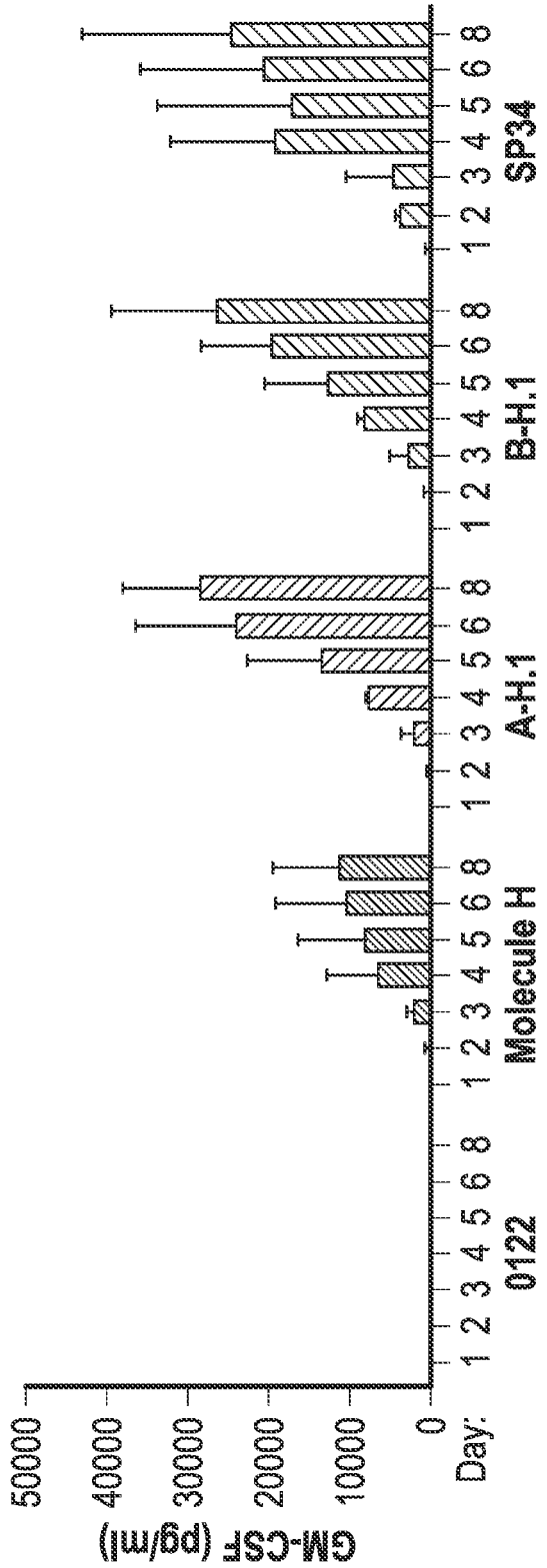

GM-CSF
GM-CSF (pg/ml)
50000
40000
30000
20000
10000
0
Day:
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27C

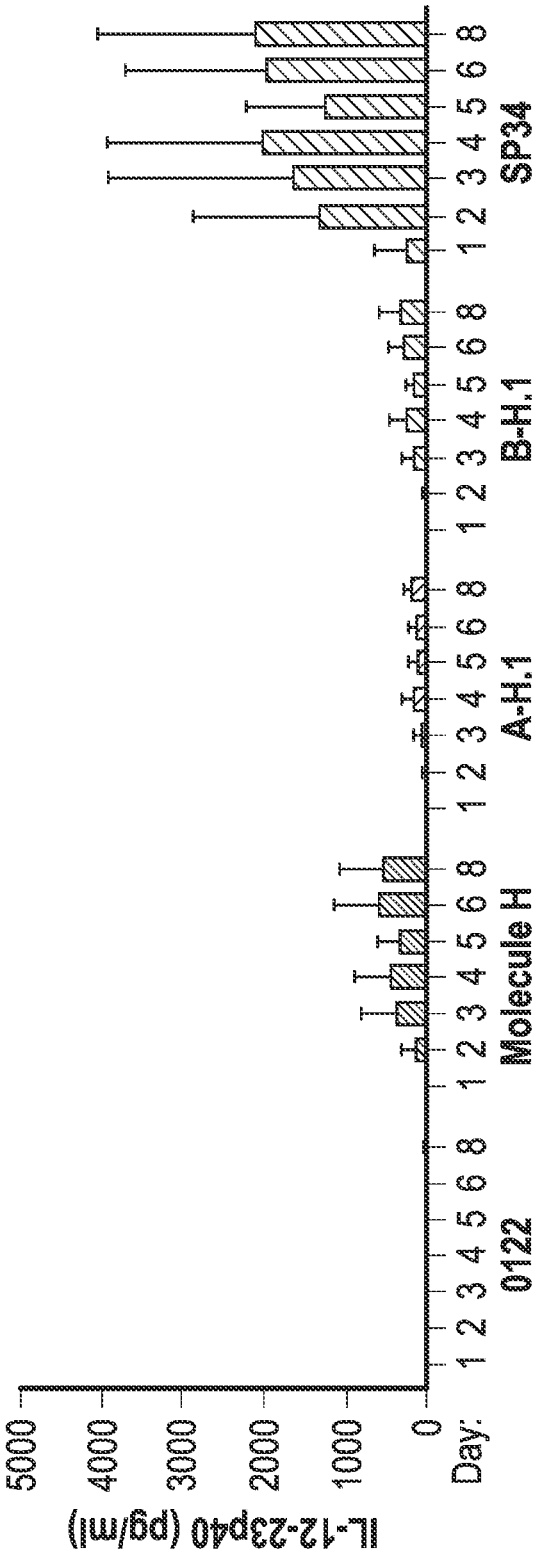

IL-12-23p40
IL-12-23p40 (pg/ml)
5000
4000
3000
2000
1000
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
Ab [100]nM
B-H.1
SP34

FIG. 27D

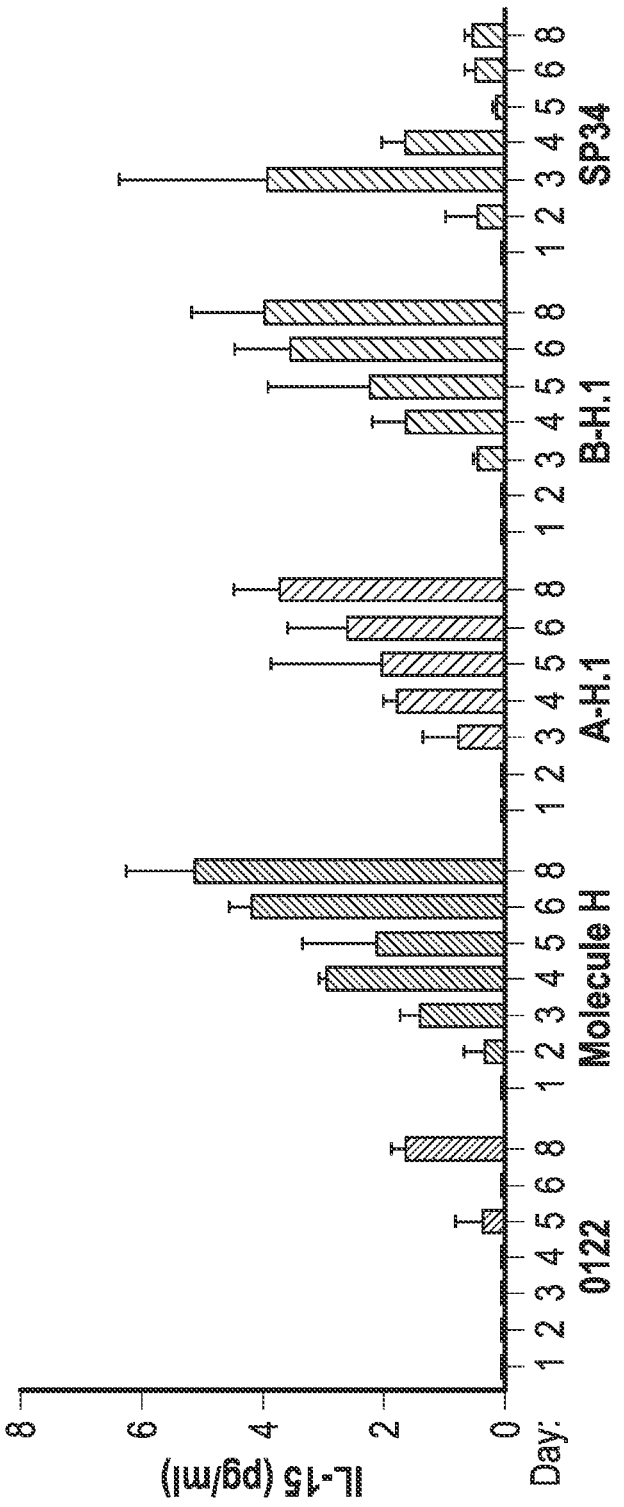

IL-15
IL-15 (pg/ml)
0
2
4
6
8
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27E

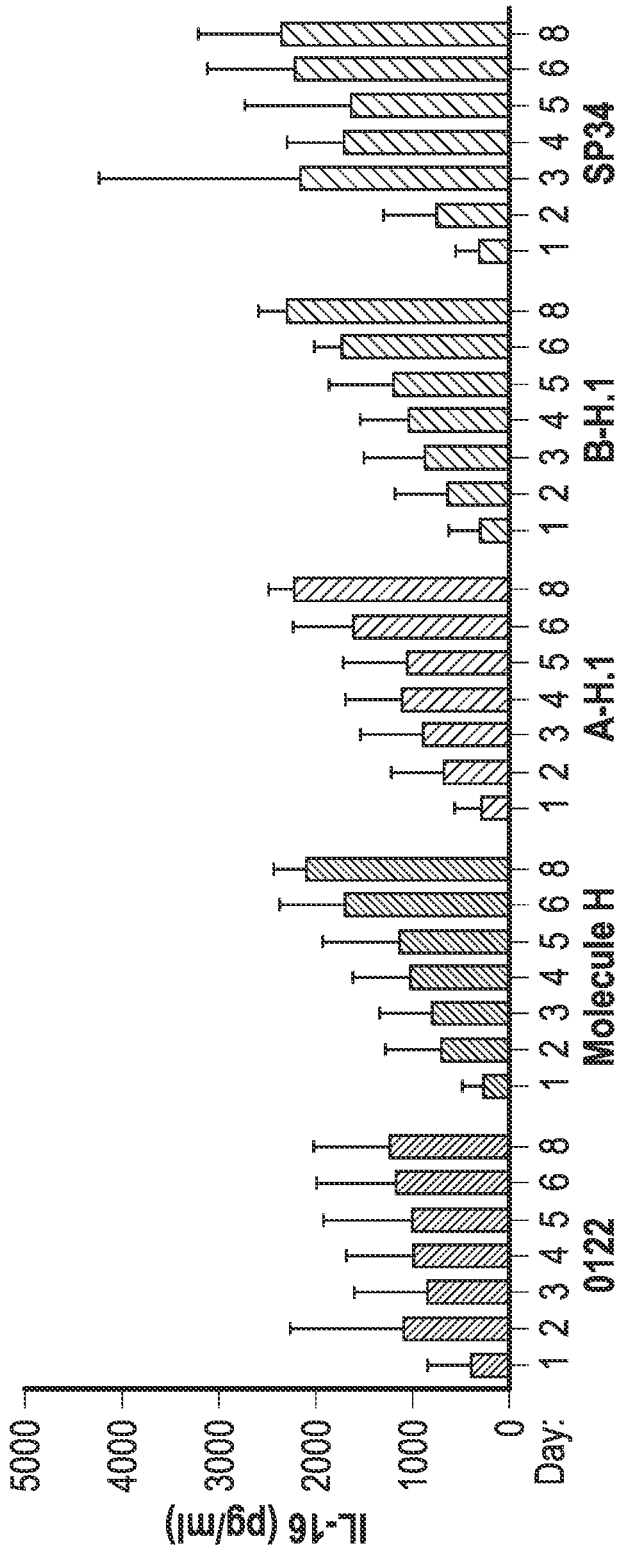

IL-16
IL-16 (pg/ml)
5000
4000
3000
2000
1000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100]nM

FIG. 27F

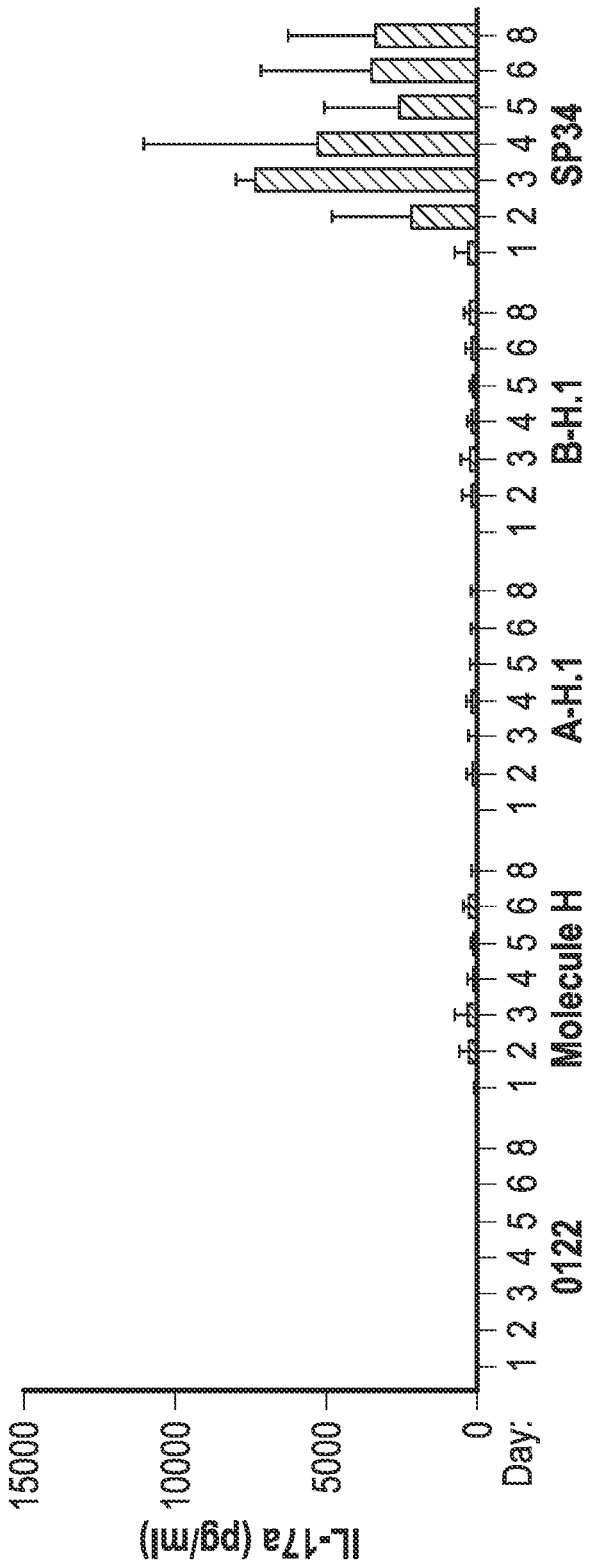

IL-17a
IL-17a (pg/ml)
15000
10000
5000
0
Day:
1 2 3 4 5 6 8
0122
1 2 3 4 5 6 8
Molecule H
1 2 3 4 5 6 8
A-H.1
1 2 3 4 5 6 8
B-H.1
1 2 3 4 5 6 8
SP34
Ab [100]nM

FIG. 27G

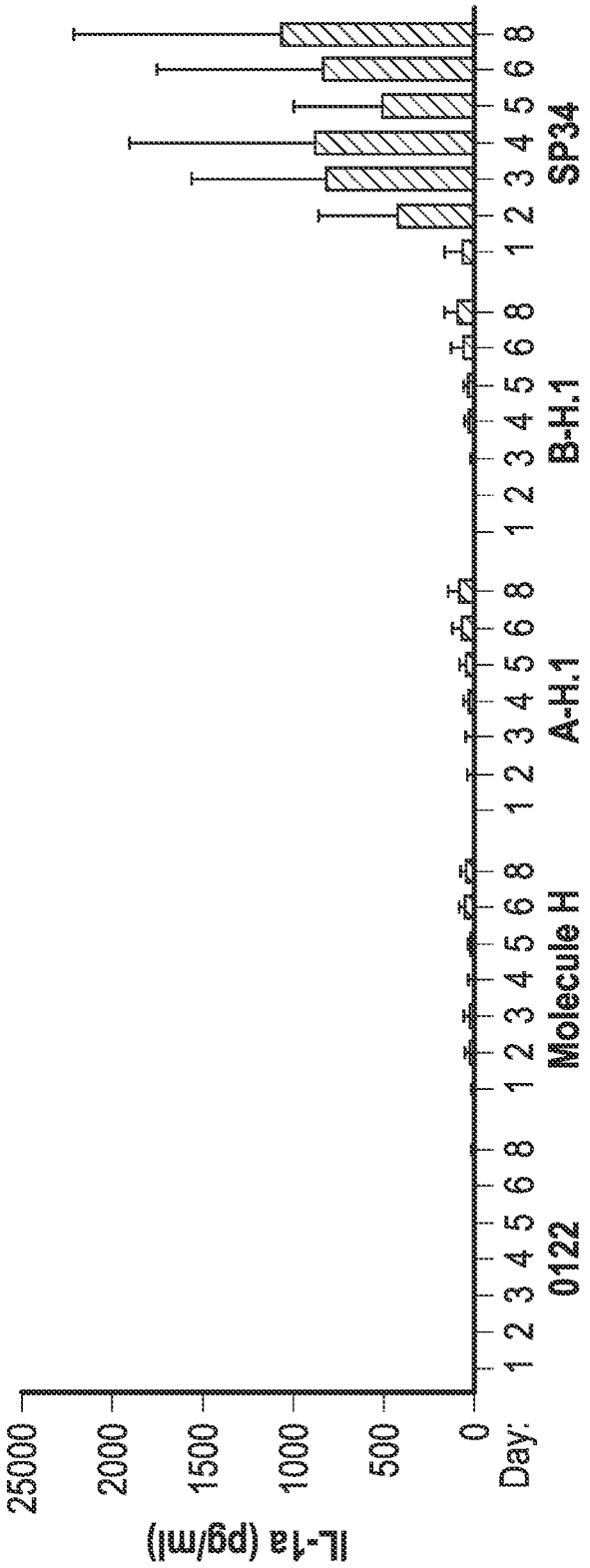

IL-1a
IL-1a (pg/ml)
25000
2000
1500
1000
500
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27H

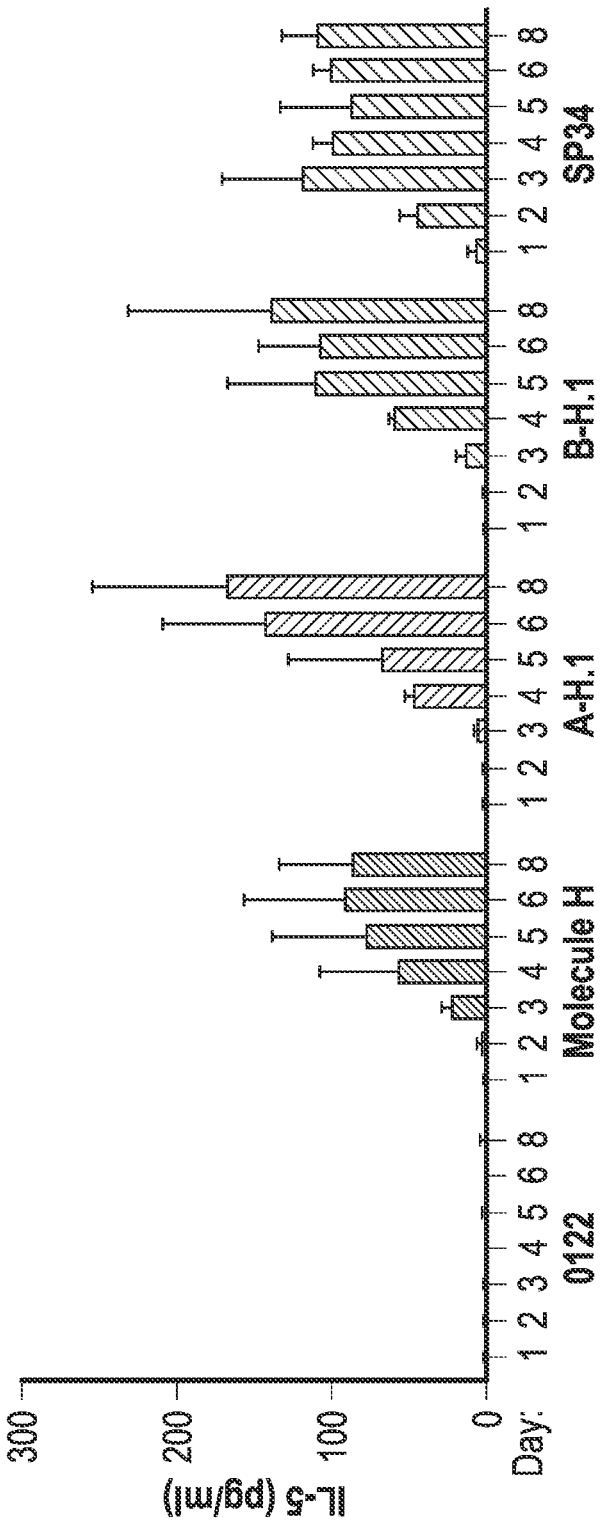

IL-5
IL-5 (pg/ml)
300
200
100
0
Day:
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM
1 2 3 4 5 6 8

FIG. 27I

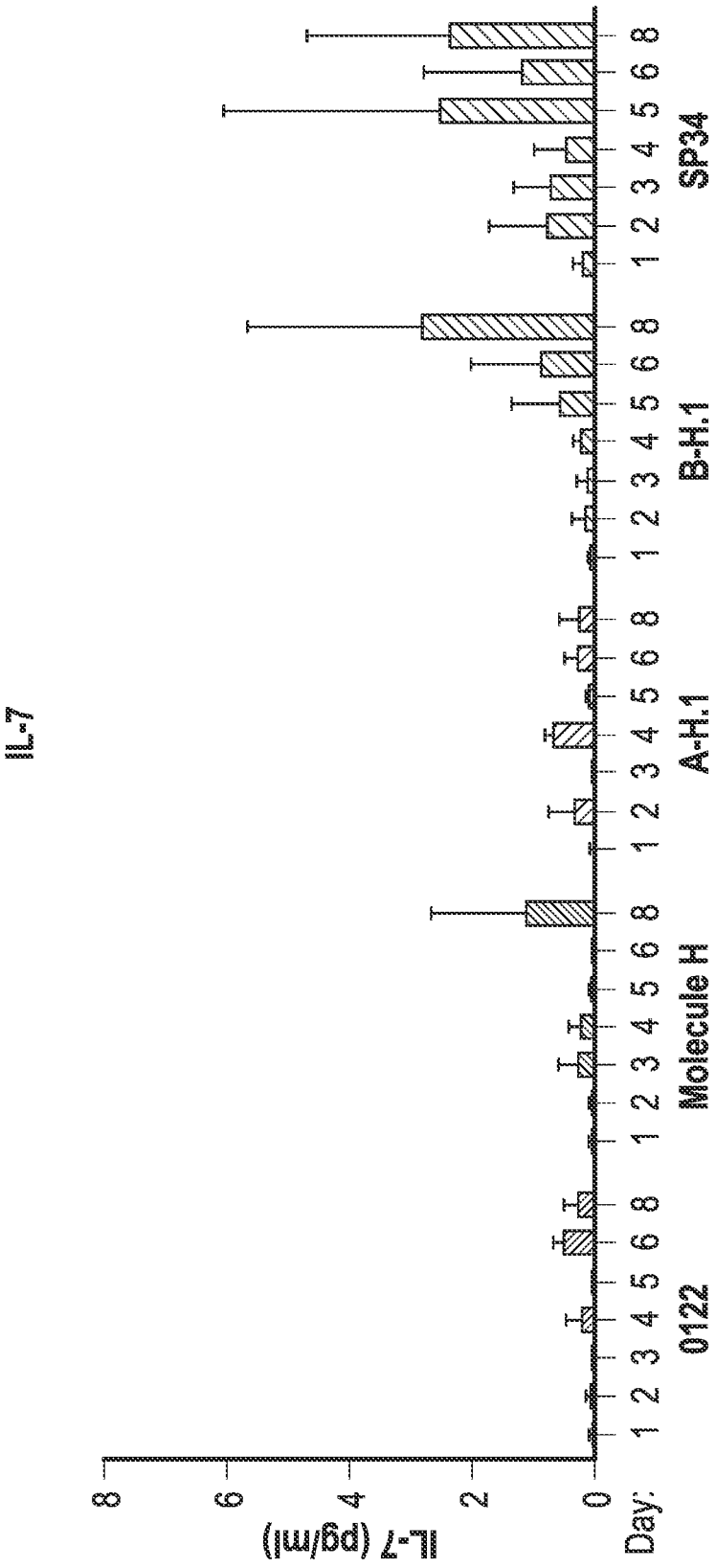


FIG. 27J

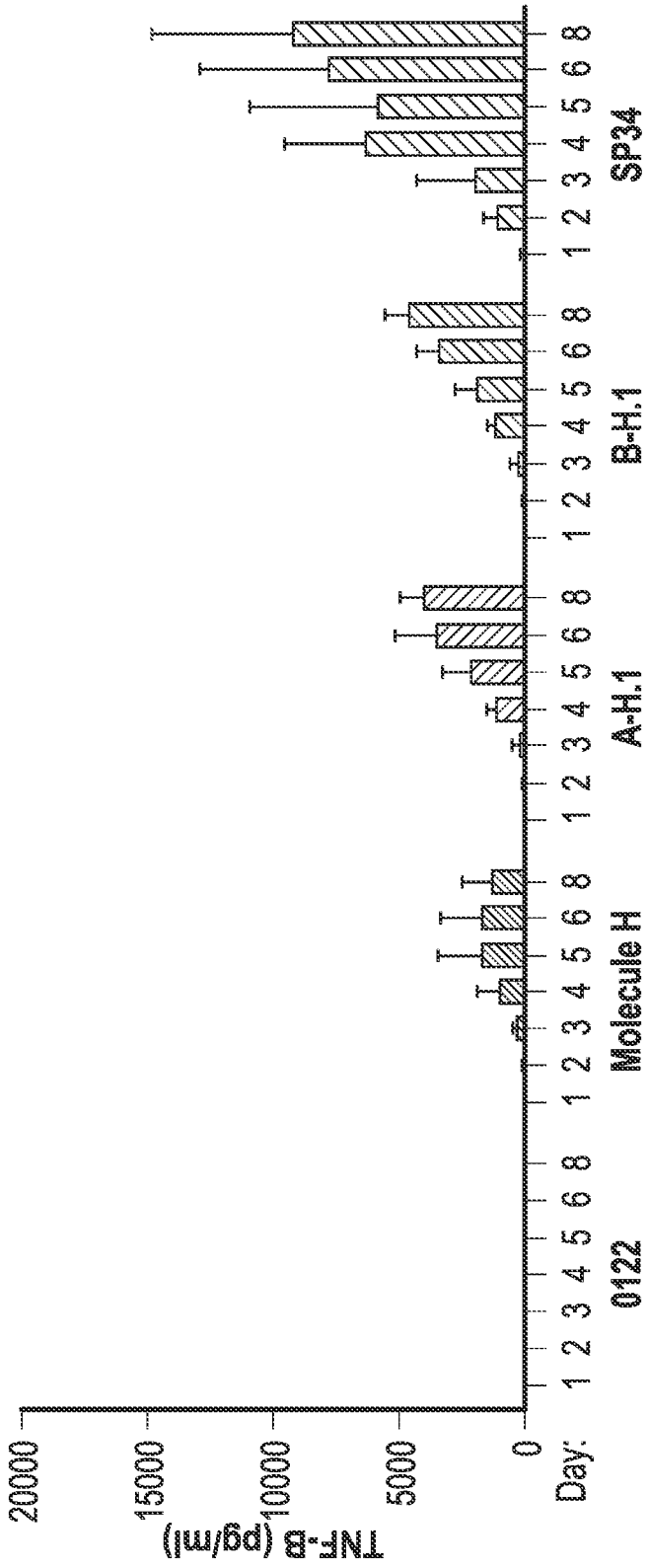

TNF-B
TNF-B (pg/ml)
20000
15000
10000
5000
0
Day:
1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27K

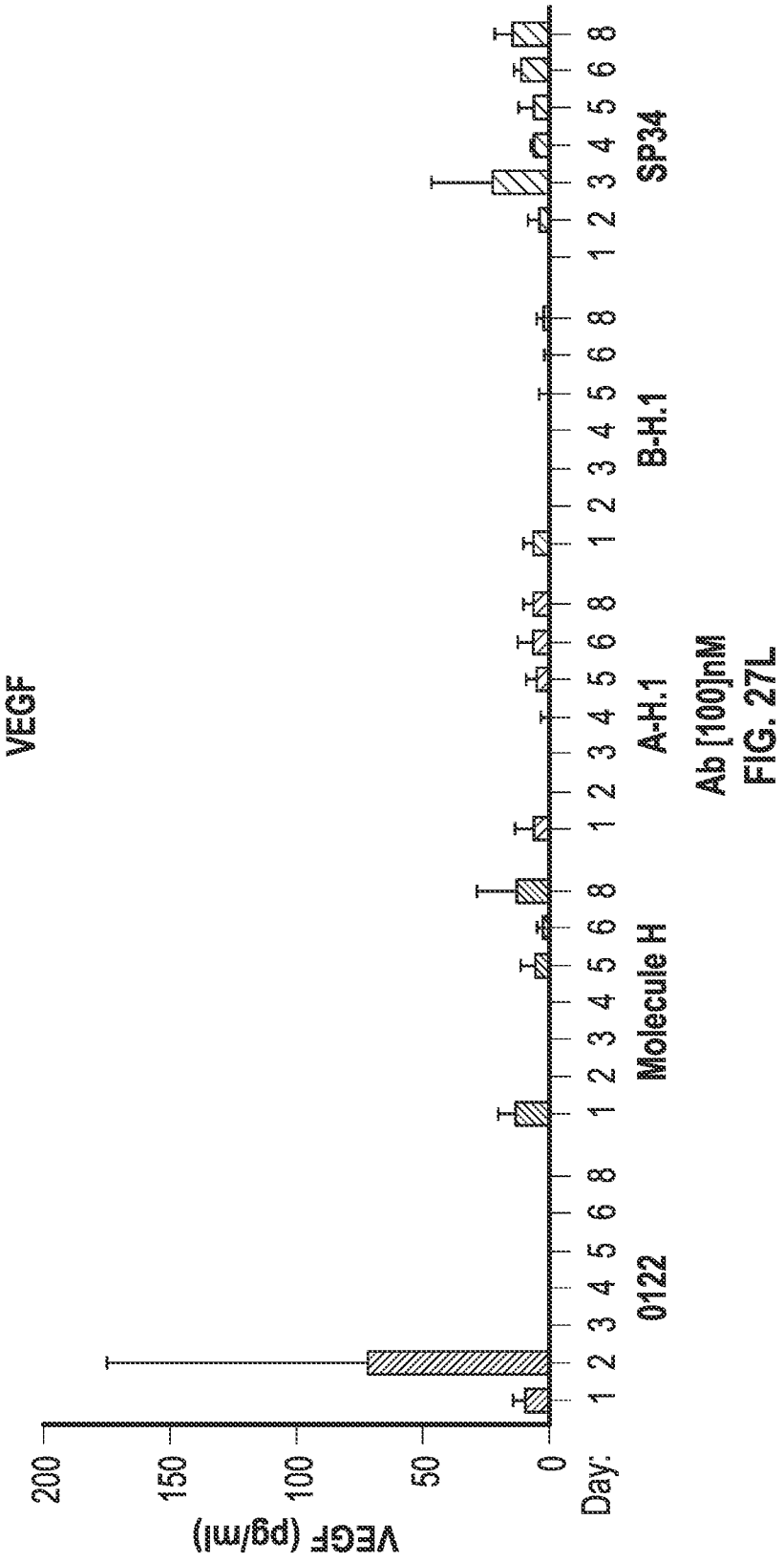

VEGF
VEGF (pg/ml)
200
150
100
50
0
Day: 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8 1 2 3 4 5 6 8
0122
Molecule H
A-H.1
B-H.1
SP34
Ab [100]nM

FIG. 27L

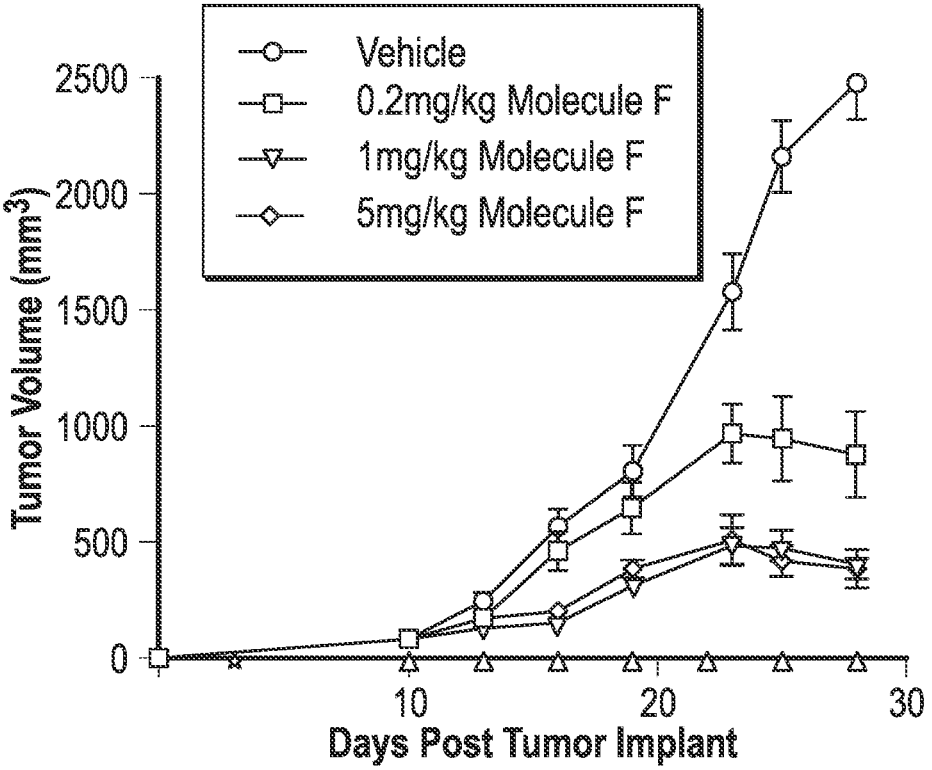

Vehicle
0.2mg/kg Molecule F
1mg/kg Molecule F
5mg/kg Molecule F
Tumor Volume (mm3)
2500
2000
1500
1000
500
0
10
20
30
Days Post Tumor Implant

FIG. 28

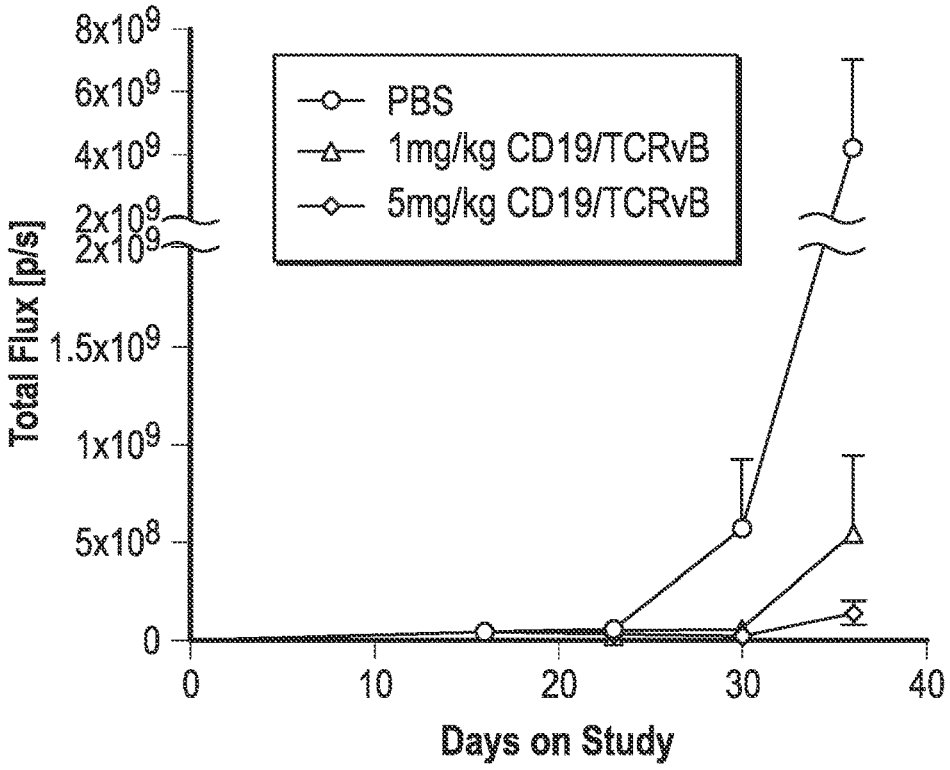


FIG. 29A

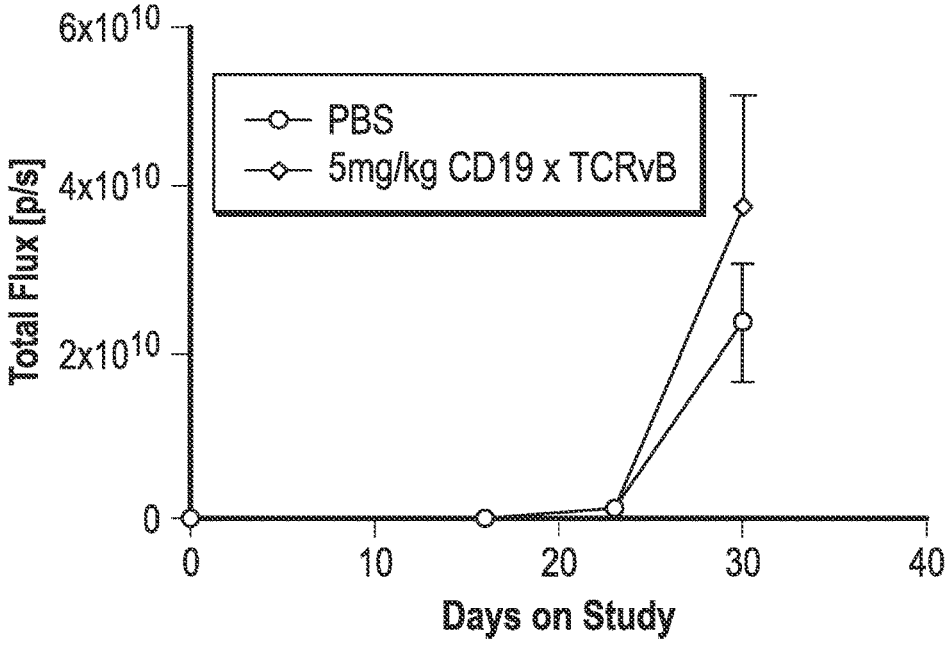


FIG. 29B

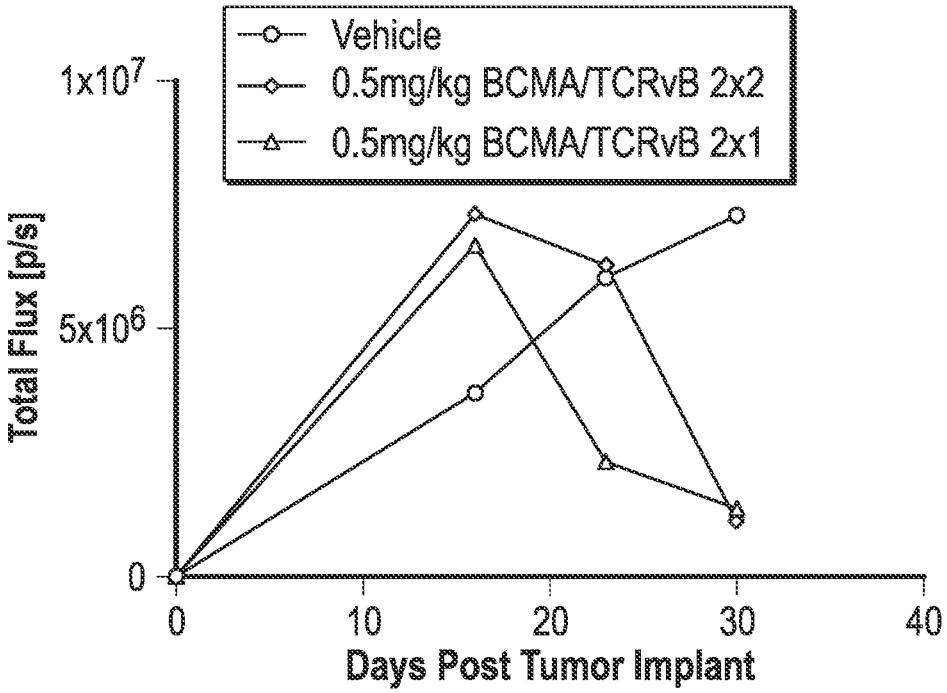
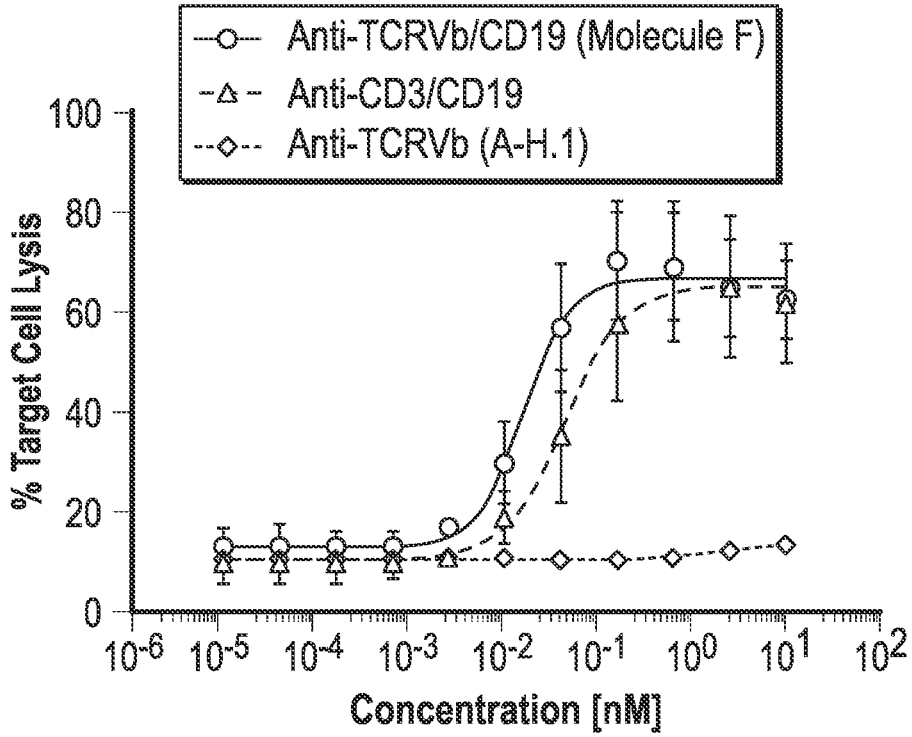
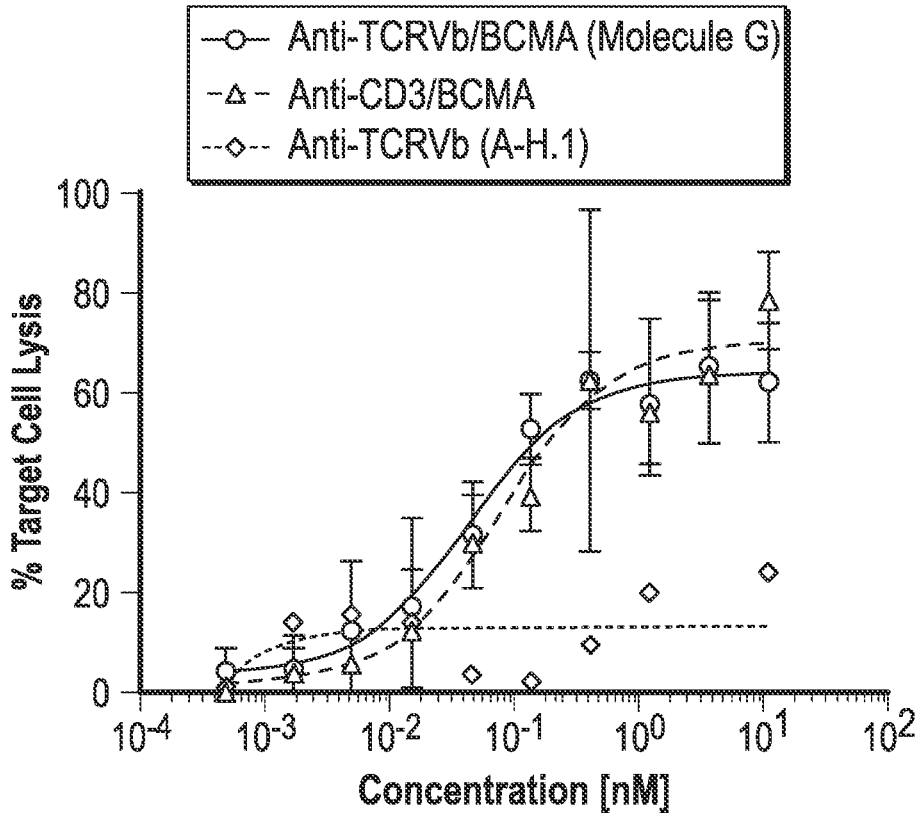


FIG. 30



	Molecule F	aCD3/CD19
IC50	0.01543	0.04246

FIG. 31A



	Molecule G	aCD3/BCMA
IC50	0.044	0.0782

FIG. 31B

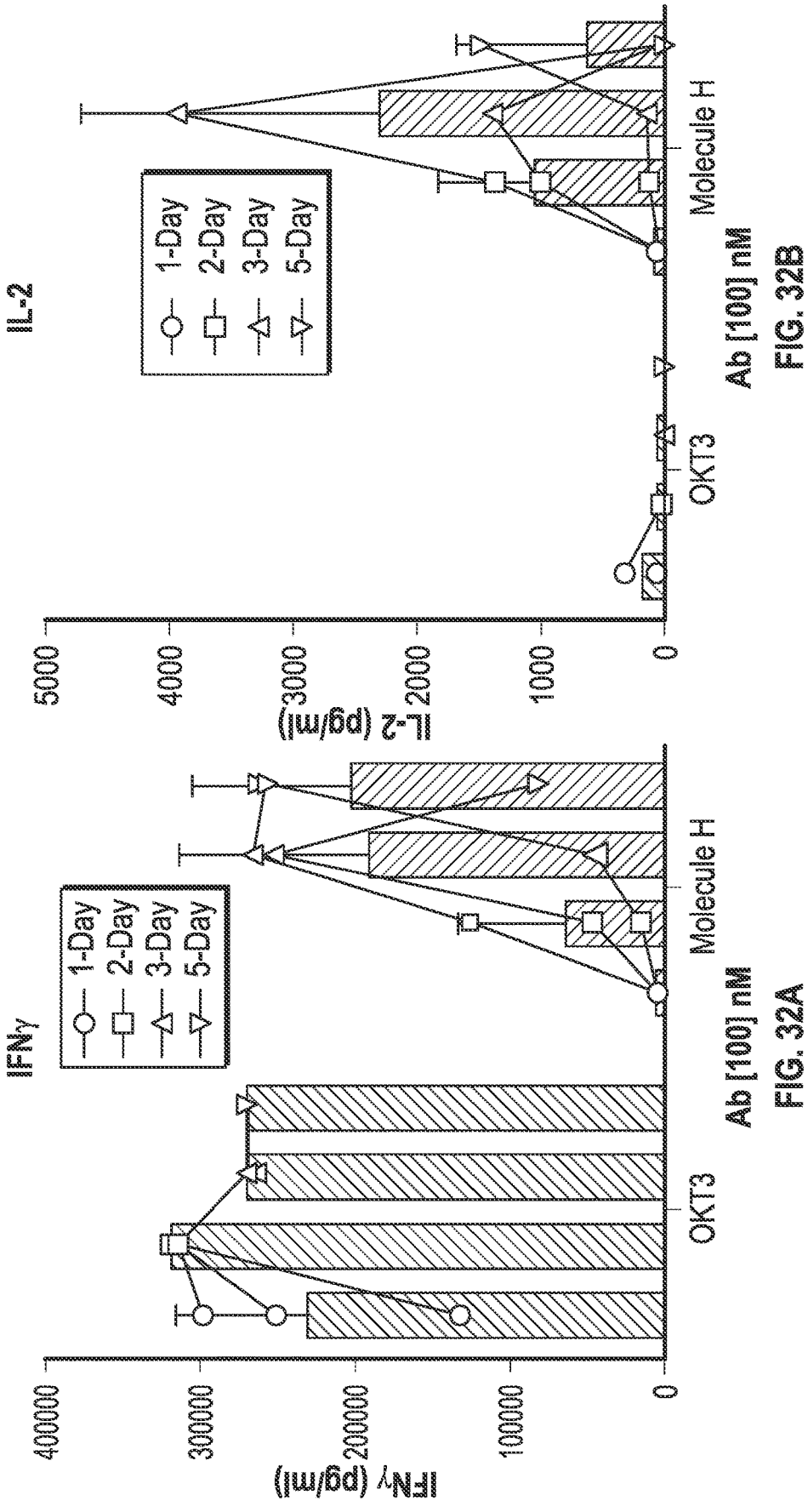


FIG. 32A

FIG. 32B

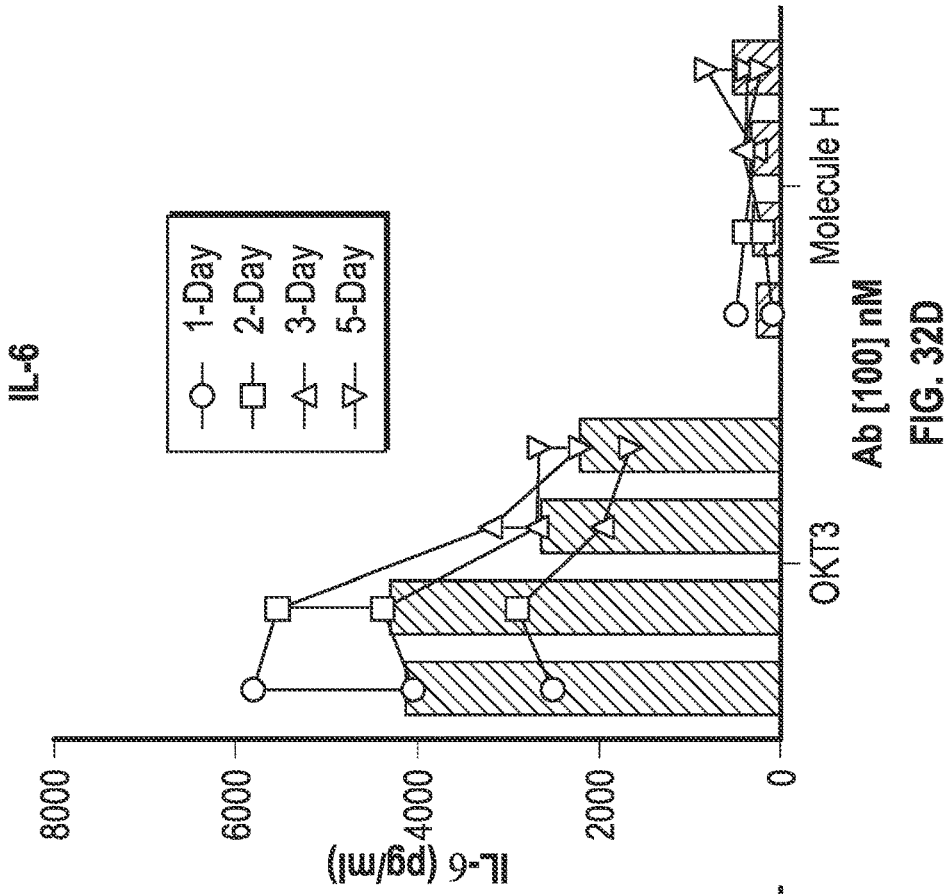


FIG. 32D

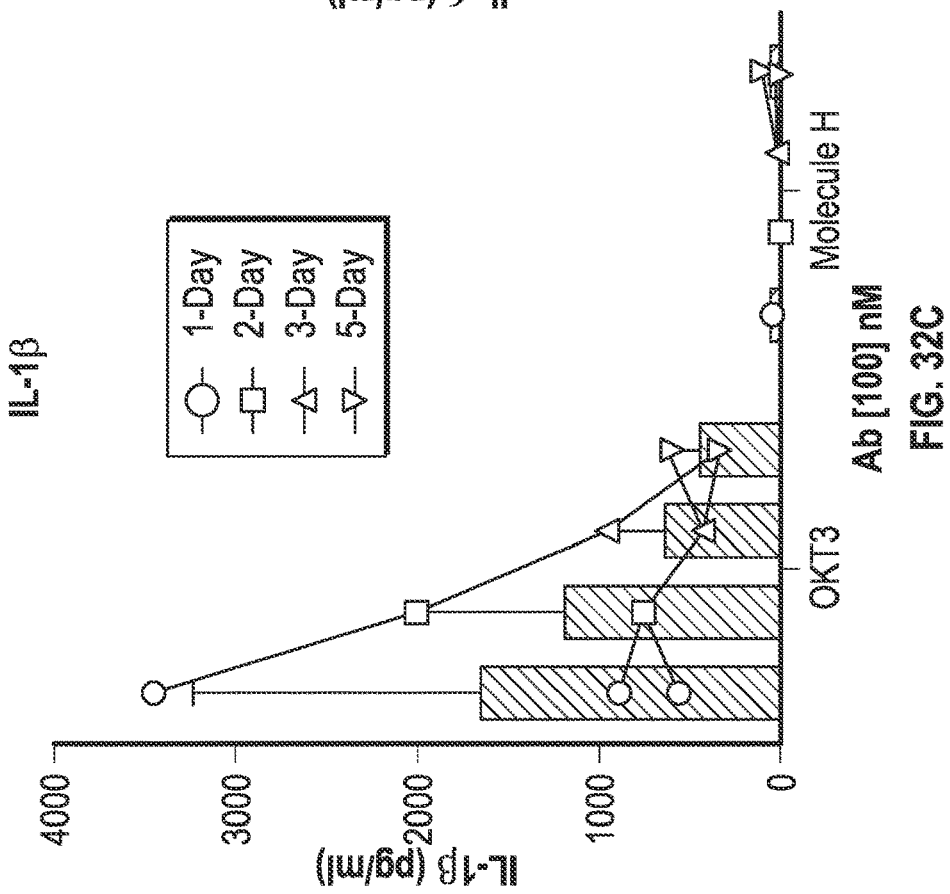


FIG. 32C

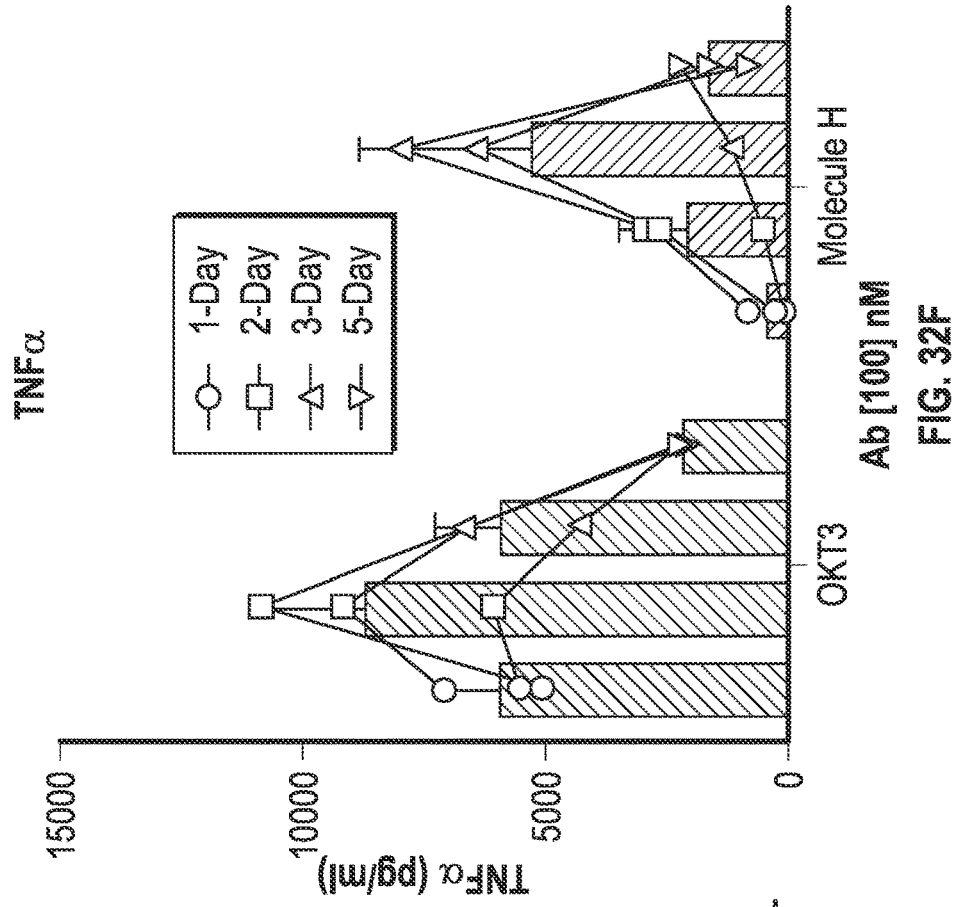


FIG. 32F

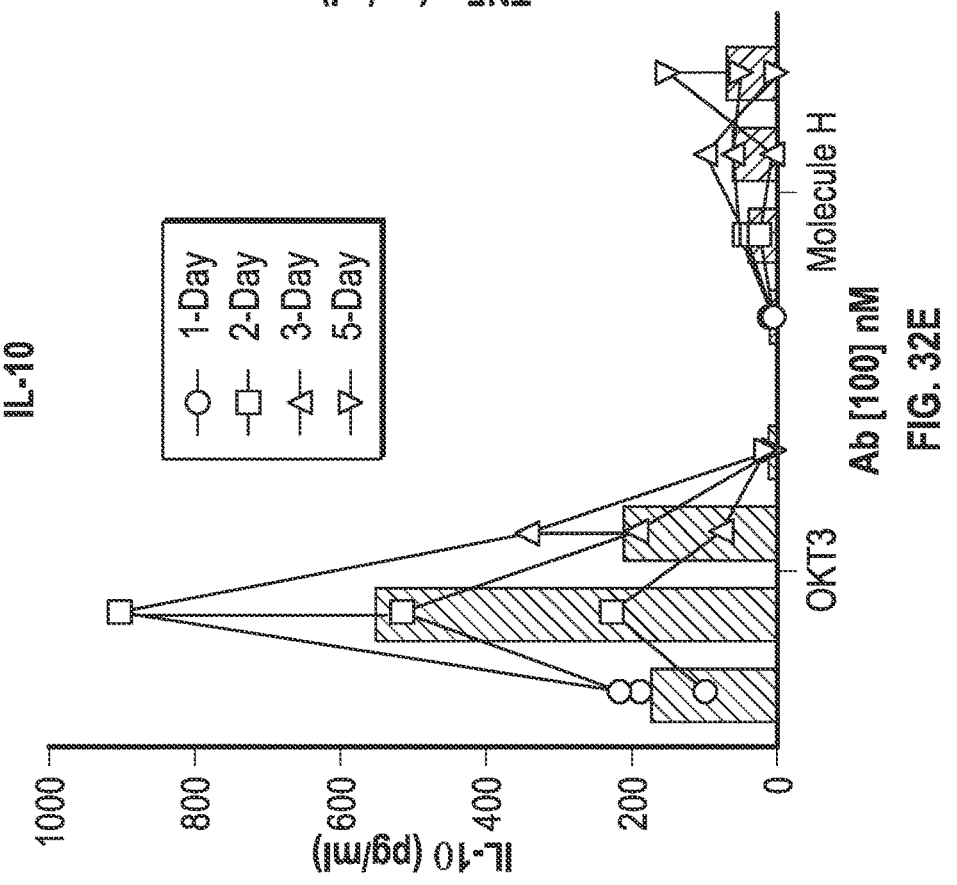


FIG. 32E

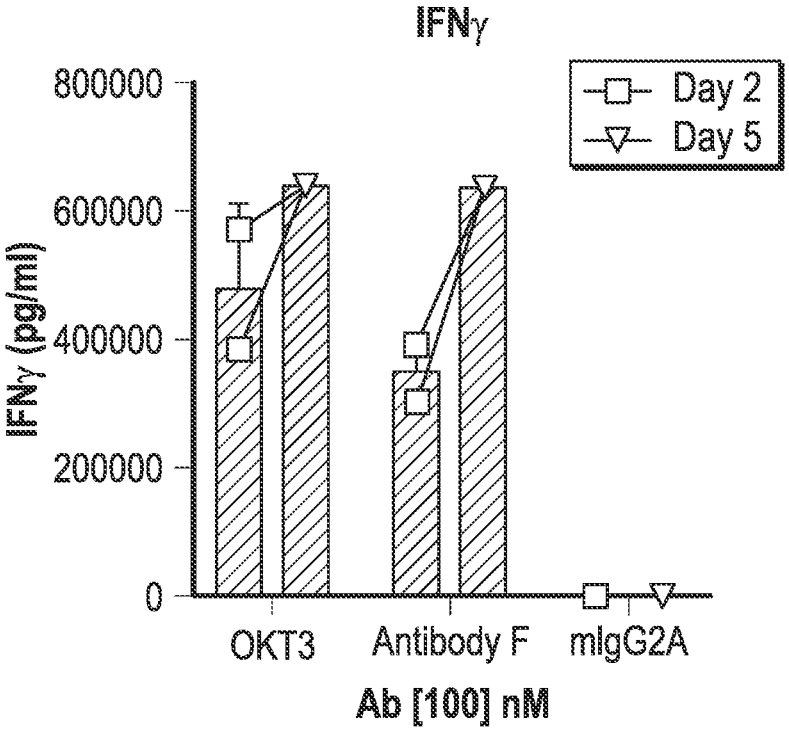


FIG. 33A

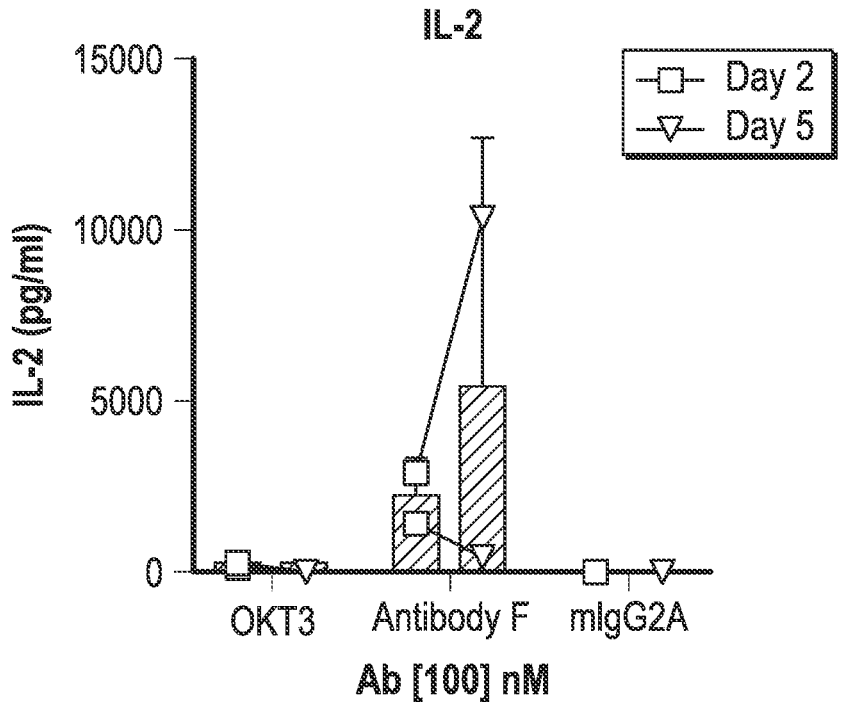


FIG. 33B

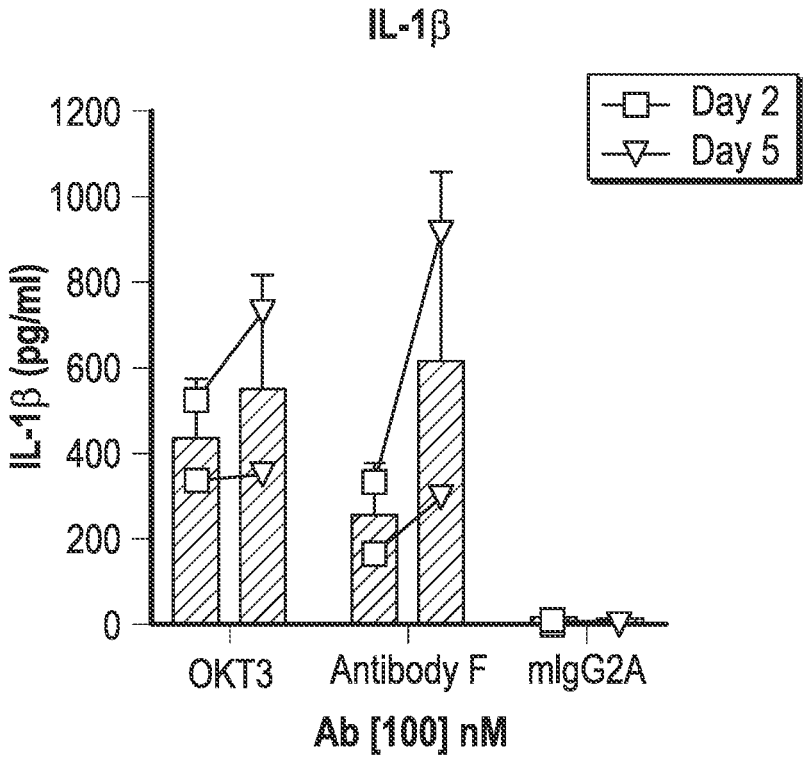


FIG. 33C

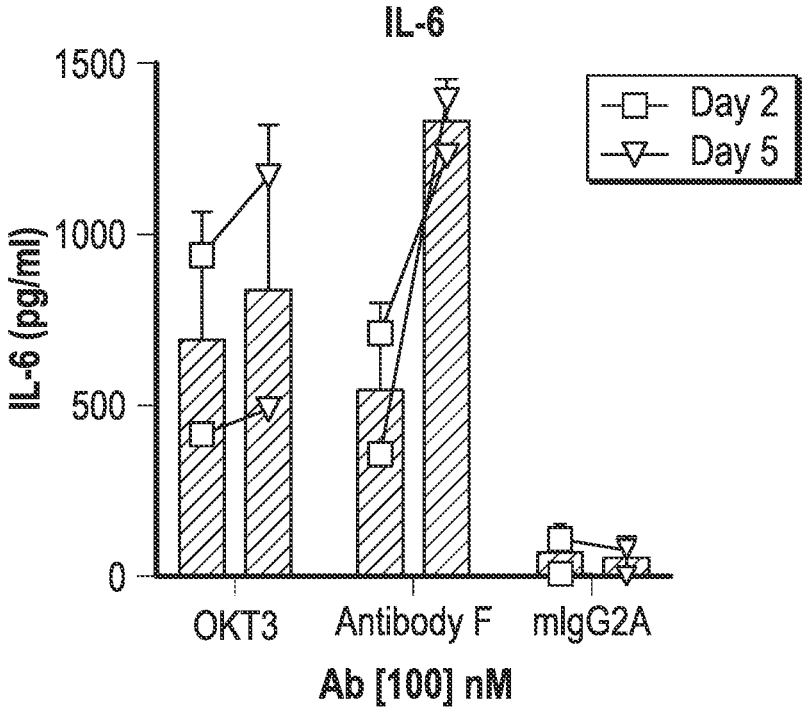


FIG. 33D

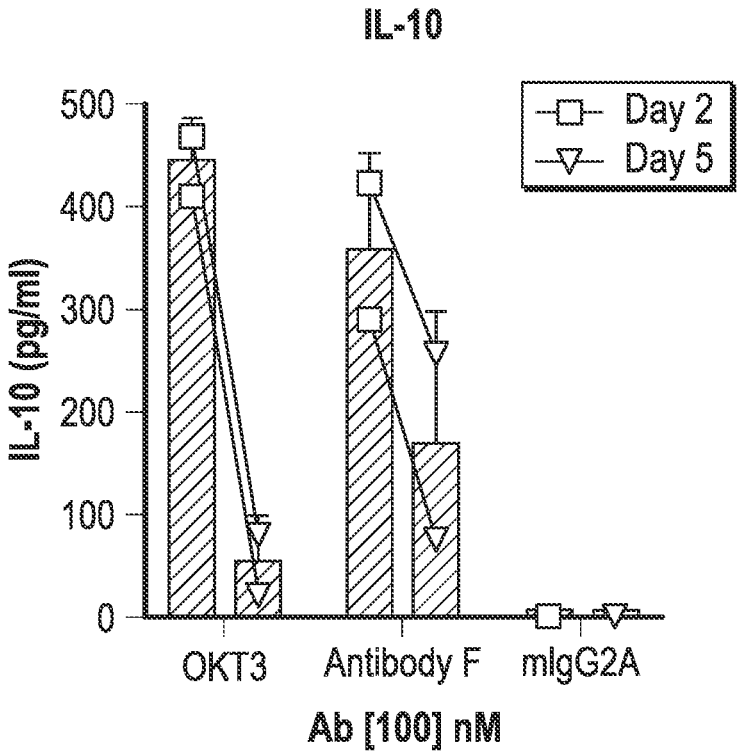


FIG. 33E

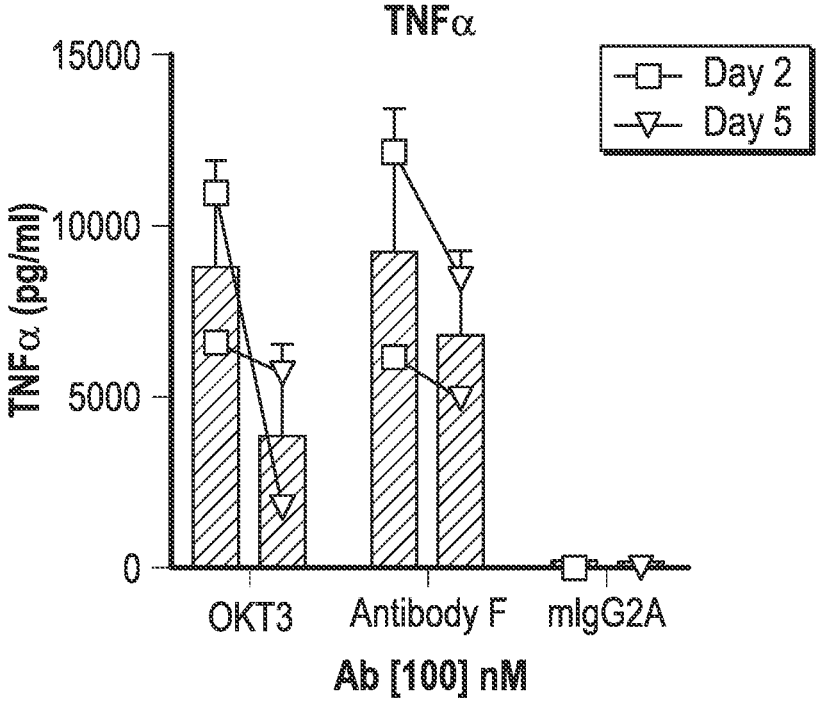


FIG. 33F

Table 9: Alignment of TCRBV amino acid sequences (SEQ ID NOS: 3457-3639, respectively, in order of appearance)

	FR1-IMGT			CDR1-IMGT		FR2-IMGT		CDR2-IMGT			FR3-IMGT					CDR3-IMGT	
	(1-26)			(27-38)		(39-55)		(56-65)			(66-104)					(105-117)	
Gene	A		B	BC		C	C'	C'C"		C"	D		E		F	FG	
	(1-15)		(16-26)	(27-38)		(39-46)	(47-55)	(56-65)		(66-74)	(75-84)		(85-96)		(97-104)		
	---------->		---------->			---------->	---------->			---------->	---------->		---------->		---------->		
	1	10	15 16	23 26 27	38	3941	46 47	55 56	65	66	74 75	84	85 89	96	97 104	105	
	|.....|....|		|.....|..|	|.....|		|.|....|	|.....|	|.....|		|.....|	|.....|		|...|.....|		|.....|	|.....
TRBV1	DTGITQTPKYLVTAM GSKRTMKREHL GH.....DS MYWYRQKA KKSLEFMFY YNC....KEF IENKTVP.N HFTPECP.DS SRLYLHVVALQQ EDSAAYLC TSSQ																
TRBV2	EPEVTQTPSHQVTQM GQEVILRCVPI SNH.....LY FYWYRQIL GQKVEFLVS FYN....NEI SEKSEIFDD QFSVERP.DG SNFTLKIRSTKL EDSAMYFC ASSE																
TRBV3-1	DTAVSQTPKYLVTQM GNDKSIKCEQN LGH.....DT MYWYKQDS KKFLKIMFS YNN....KEL IINETVP.N RFSPKSP.DK AHLNLHINSLEL GDSAVYFC ASSQ																
TRBV3-2	DTAVSQTPKYLVTQM GRKESLK*EQN LGH.....NA MYWYKQDS KKFLKTMFI YSN....KEP ILNETVP.N RFSPDSP.DK AHLNLHINSLEL GDSAVYFC ASSQ																
TRBV4-1	DTEVTQTPKHLVMGM TNKKSLKCEQH MGH.....RA MYWYKQKA KKPPELMFV YSY....EKL SINESVP.S RFSPECP.NS SLLNLHLHALQP EDSALYLC ASSQ																
TRBV4-2	ETGVTQTPRHLVMGM TNKRSLKCEQH LGH.....NA MYWYRQSA KKPLELMFV YNF....KEQ TENNSVP.S RFSPECP.NS SHLFLHLHTLQP EDSALYLC ASSQ																
TRBV4-3	ETGVTQTPRHLVMGM TNKKSLKCEQH LGH.....NA MYWYKQSA KKPLELMFV YSL....EER VENNSVP.S RFSPECP.NS SHLFLHLHTLQP EDSALYLC ASSQ																
TRBV5-1	KAGVTQTPRYLIKTR GQQVTLSCSPI SGH.....RS VSWYQQTP GQGLQFLFE YFS....ETQ RNKGNFP.G RFSGRQF.SN SRSEMNVSTLEL GDSALYLC ASSL																
TRBV5-3	EAGVTQSPTHLIKTR GQQVTLRCSPI SGH.....SS VSWYQQAP GQGPQFIFE YAN....ELR RSEGNFP.N RFSGRQF.HD CCSEMNVSALEL GDSALYLC ARSL																
TRBV5-4	ETGVTQSPTHLIKTR GQQVTLRCSSQ SGH.....NT VSWYQQAL GQGPQFIFQ YYR....EEE NGRGNFP.P RFSGLQF.PN YSSELNVNALEL DDSALYLC ASSL																
TRBV5-5	DAGVTQSPTHLIKTR GQQVTLRCSPI SGH.....KS VSWYQQVL GQGPQFIFQ YYE....KEE RGRGNFP.D RFSARQF.PN YSSELNVNALLL GDSALYLC ASSL																
TRBV5-6	DAGVTQSPTHLIKTR GQQVTLRCSPK SGH.....DT VSWYQQAL GQGPQFIFQ YYE....EEE RQRGNFP.D RFSGHQF.PN YSSELNVNALLL GDSALYLC ASSL																
TRBV5-7	DAGVTQSPTHLIKTR GQHVTLRCSPI SGH.....TS VSSYQQAL GQGPQFIFQ YYE....KEE RGRGNFP.D QFSGHQF.PN YSSELNVNALLL GDSALYLC ASSL																
TRBV5-8	EAGVTQSPTHLIKTR GQQATLRCSPI SGH.....TS VYWYQQAL GLGLQFLLW YDE....GEE RNRGNFP.P RFSGRQF.PN YSSELNVNALEL EDSALYLC ASSL																
TRBV6-1	NAGVTQTPKFQVLKT GQSMTLQCAQD MNH.....NS MYWYRQDP GMGLRLIYY SAS....EGT TDKGEVP.N GYNVSRL.NK REFSLRLESAAP SQTSVYFC ASSE																
TRBV6-2	NAGVTQTPKFRVLKT GQSMTLLCAQD MNH.....EY MYWYRQDP GMGLRLIHY SVG....EGT TAKGEVP.D GYNVSRL.KK QNFLLGLESAAP SQTSVYFC ASSY																
TRBV6-3	NAGVTQTPRFRVLKT GQSMTLLCAQD MNH.....EY MYWYRQDP GMGLRLIHY SVG....EGT TAKGEVP.D GYNVSRL.KK QNFLLGLESAAP SQTSVYFC ASSY																
TRBV6-4	IAGITQAPTSQILAA GRPMTLRCTQD MRH.....NA MYWYRQDL GLGLRLIHY SNT....AGT TGKGEVP.D GYSVSRA.NT DDFPLTLASAVP SQTSVYFC ASSD																

FIG. 34

TRBV6-5	NAGVTQTPKFQVLKT GQSMTLQCAQD MNH.....EY MSWYRQDP GMGLRLIHY SVG....AGI TDQGEVP.N GYNVSRS.FT EDFPLRLLSAAP SQTSVYFC ASSY
TRBV6-6	NAGVTQTPRFRILKI GQSMTLQCTQD MNH.....NY MYWYRQDP GMGLKLIYY SVG....AGI TDKGEVP.N GYNVSRS.TT EDFPLRLLAAP SQTSVYFC ASSY
TRBV6-7	NAGVTQTPRFHVLKT GQSMTLLCAQD MNH.....EY MYRYRQDP GKGLRLIYY SVA....AAL TDKGEVP.N GYNVSRS.NT EDFPLKLESAAP SQTSVYFC ASSY
TRBV6-8	NAGVTQTPKFHILKT GQSMTLQCAQD MNH.....GY MSWYRQDP GMGLRLIYY SAA....AGT TDK.EVP.N GYNVSRL.NT EDFPLRLVSAAP SQTSVYLC ASSY
TRBV6-9	NAGVTQTPRFHILKT GQSMTLQCAQD MNH.....GY LSWYRQDP GMGLRRIHY SVA....AGI TDKGEVP.D GYNVSRS.NT EDFPLRLESAAP SQTSVYFC ASSY
TRBV7-1	GAGVSQSLPNKVAKK GKDVALRYDPI SGH.....NA LYWYRQSL GQGLEFIIY FQG....KDA ADKSGLPRD RFSAQRS.EG SISTLKFQRTQQ GDLAVYLC ASSS
TRBV7-2	GAGVSQSPSNKVTEK GKDVELRCDPI SGH.....TA LYWYRQSL GQGLEFLIY FQG....NSA PDKSGLPSD RFSAERT.GG SVSTLTIQRTQQ EDSAVYLC ASSL
TRBV7-3	GAGVSQTPSNKVTEK GKNVELRCDPI SGH.....TA LYWYRQSL GQGPEFLIY FQG....TGA ADDSGLPND RFEAVRP.EG SVSTLKIQRTER GDSAVYLC ASSL
TRBV7-4	GAGVSQSPRYKVAKR GRDVALRCDSI SGH.....VT LYWYRQTL GQGSEVLTY SQS....DAQ RDKSGRPSG RFSAERP.ER SVSTLKIQRTEQ GDSAVYLC ASSL
TRBV7-6	GAGVSQSPRYKVTKR GQDVALRCDPI SGH.....VS LYWYRQAL GQGPEFLTY FNY....EAQ QDKSGLPND RFSAERP.EG SISTLTIQRTEQ RDSAMYRC ASSL
TRBV7-7	GAGVSQSPRYKVTKR GQDVTLRCDPI SSH.....AT LYWYQQAL GQGPEFLTY FNY....EAQ PDKSGLPSD RFSAERP.EG SISTLTIQRTEQ RDSAMYRC ASSL
TRBV7-8	GAGVSQSPRYKVAKR GQDVALRCDPI SGH.....VS LFWYQQAL GQGPEFLTY FQN....EAQ LDKSGLPSD RFEAERP.EG SVSTLKIQRTQQ EDSAVYLC ASSL
TRBV7-9	DTGVSQNPRHKITKR GQNVTFRCDPI SEH.....NR LYWYRQTL GQGPEFLTY FQN....EAQ LEKSRLLSD RFSAERP.KG SFSTLEIQRTEQ GDSAMYLC ASSL
TRBV9	DSGVTQTPKHLITAT GQRVTLRCSPR SGD.....LS VYWYQQSL DQGLQFLIQ YYN....GEE RAKGNIL.E RFSAQQF.PD LHSELNLSSLEL GDSALYFC ASSV
TRBV10-1	DAEITQSPRHKITET GRQVTLACHQT WNH.....NN MFWYRQDL GHGLRLIHY SYG....VQD TNKGEVS.D GYSVSRS.NT EDLPLTLESAAS SQTSVYFC ASSE
TRBV10-2	DAGITQSPRYKITET GRQVTLMCHQT WSH.....SY MFWYRQDL GHGLRLIYY SAA....ADI TDKGEVP.D GYVVSRS.KT ENTPLTLESATR SQTSVYFC ASSE
TRBV10-3	DAGITQSPRHKVTET GN2VTLRCHQT ENH.....RY MYWYRQD2 GHGLRLIHY SYG....VKD TDKGEVS.D GYSVSRS.KT EDELLTLESATS SQTSVYFC AISE
TRBV11-1	EAEVAQSPRYKITEK SQAVAFWCDPI SGH.....AT LYWYRQIL GQGPELLVQ FQD....ESV VDDSQLPKD RFSAERL.KG VDSTLKIQPAEL GDSAMYLC ASSL
TRBV11-2	EAGVAQSPRYKIIEK RQSVAFWCNPI SGH.....AT LYWYQQIL GQGPKLLIQ FQN....NGV VDDSQLPKD RFSAERL.KG VDSTLKIQPAKL EDSAVYLC ASSL
TRBV11-3	EAGVVQSPRYKIIEK KQPVAFWCNPI SGH.....NT LYWYLQNL GQGPELLIR YFN....EEA VDDSQLPKD RFSAERL.KG VDSTLKIQPAEL GDSAVYLC ASSL
TRBV12-1	DAGVIQSPRHKVTEM GQSVTLRCEPI SGH.....ND LAWYRQTF VQGLELLNY FCS....WTL VDDSGVSKD *FSAQMP.DV SFSTRIQPMEP RDLGLYFC ASSF
TRBV12-2	DAGIIQSPKHEVTEM GQTVTLRCEPI FGH.....NF LFWYRDTF VQGLELLSY FPS....*SI IDNAGMPTE RFSAERP.DG SFSTLKIQPAEQ GDSAVYVC ASRL
TRBV12-3	DAGVIQSPRHEVTEM GQEVTLRCKPI SGH.....NS LFWYRQTM MRGLELLIY FNN....MVP IDDSGMPED RFSAKMP.NA SFSTLKIQPSEP RDSAVYFC ASSL
TRBV12-4	DAGVIQSPRHEVTEM GQEVTLRCKPI SGH.....DY LFWYRQTM MRGLELLIY FNN....MVP IDDSGMPED RFSAKMP.NA SFSTLKIQPSEP RDSAVYFC ASSL
TRBV12-5	DAVVTQTPRHKVTEM GQEVTMRCQPI LGH.....NT VFWYRQTM MQGLELLAY FRN....RAP LDDSGMPKD RFSAEMP.DA TLATLKIQPSEP RDSAVYFC ASGL
TRBV13	AAGVIQSPRHLIKEK RETATLKCYPI PRH.....DT VYWYQQGQ GQDPQFLIS FYE....KMQ SDKGSIP.D RFSAQQF.SD YHSELNMSSLEL GDSALYFC ASSL
TRBV14	EAGVTQTPSHSVIEK GQTVTLRCDPI SGH.....DN LYWYRQVM GKEIKFLLH FVA....ESK QDESGMPNR RFLAERT.GG TYSTLKVQPAEL EDSGVYFC ASSQ
TRBV15	DAMVIQNPRYQVTQF GKPVTLSCSQT LNH.....NV MYWYQQKS SQAPKLLFH YVD....KDF NNEADTP.D NFQSRRP.NT SFCFLDIRSPGL GDTAMYLC AISR

FIG. 34 (continued)

TRBV16	GEEVAQTPKHLVRGE GQKAKLYCAPI KGH.....SY VFWYQQVL KNEFKFLIS FQN....ENV FDETGMPKE RFSAKCL.PN SPCSLEIQATKL EDSAVYFC ASSQ
TRBV17	EPGVSQTPRHKVTNM GQEVILRCDPS SGH.....MF VHWYRQNL RQEMKLLIS FQY....QNI AVDSGMPKE RFTAERP.NG TFSTLKIHPAEP RDSAVYLY SSG
TRBV18	NAGVMQNPRHLVRRR GQEARLRCSPM KGH.....SH VYWYRQLP EEGLKFMVY LQK....ENI IDESGMPKE RFSAERP.KE GPSILRIQQVVR GDSAAYFC ASSP
TRBV19	DGGITQSPKYLFRKE GQNVTLSCEQN LNH.....DA MYWYRQDP GQGLRLIYY SQI....VND FQKGDIA.E GYSVSRE.KK ESFPLTVTSAQK NPTAFYLC ASSI
TRBV20-1	GAVVSQHPSWVICKS GTSVKIECRSL DFQ.....ATT MFWYRQFP KQSLMLMAT SNEG...SKA TYEQGVEKD KFLINHA.SL TLSTLTVTSAHP EDSSFYIC SAR
TRBV21-1	DTKVTQNPRLLVKAS EQKARMDCVFI KAH.....SY VYWYRKKL EEELKFLVY FQN....EEL IQKAEIINE RFLAQCS.KN SSCTLEIQSTES GDTALYIC ASSK
TRBV23-1	HAKVTQTPGHLVKGK GQKTKMDCTPE KGH.....TF VYWYQQNQ NKEFMLLIS FQN....EQV LQETEMHKK RFSSQC2.KN APCSLAILSSEP GDTALYLC ASSQ
TRBV24-1	DADVTQTPRNRITKT GKPIMLECSQT KGH.....DR MYWYRQDP GLGLRLIYY SFD....VKD INKGEES.D GYSVSRQ.AQ AKFSLSLESAIP NQTALYFC ATSDL
TRBV25-1	EADIYQTPRYLVIGT GKKITLECSQT MGH.....DK MYWYQQDP GMELHLIHY SYG....VNS TEKGDLS.S ESTVSRI.RT EHFPLTLESARP SHTSQYLC ASSE
TRBV26	DAVVTQFPRHRIIGT GKEFILQCSQN MNH.....VT MYWYRQDP GLGLKLVYY SFG....TGS TEKGDIS.E GYHVS*N.TI ASFPLTLKSAST NQTSVYLY ASSS
TRBV27	EAQVTQNPRYLITVT GKKLTVTCSQN MNH.....EY MSWYRQDP GLGLRQIYY SMG....VEV TDKGDVP.E GYKVSRK.EK FNFPLILESPSP NQTSLYFC ASSL
TRBV28	DVEVTQSSRYLVKRT GEKVFLECVQD MDH.....EN MFWYRQDP GLGLRLIYF SYD....VKM KEKGDIP.E GYSVSRE.KK ERFSLILESAST NQTSMYLC ASSL
TRBV29-1	SAVISQKPSRDICQR GTSLTIQCQVD SQV.....TM MFWYRQQP GQSLTLIAT ANQG...SEA TYESGFVID KFPISRP.NL TFSTLTVSNMSP EDSSIYLC SVE
TRBV30	SQTTHQWATLVQPV GSPLSLECTVE GTS.....NPN LYWYRQAA GRGLQLLFY SVG.....IG QISSFVP.Q NLSASRP.QD RQFILSSKKLLL SDSGFYLC AWS

FIG. 34 (continued)

Alignment of affinity matured humanized Antibody A-H VL sequences (SEQ ID NOS 3377-3389, respectively, in order of appearance)

```
a5-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVENKVAWHQQKPGKAPKALIYSSSHRYKGVPS   60
c1d2d4-VL                          DIQMTQSPSFLSASVGDRVTITCKASQNVDNKVAWHQQKPGKAPKALIYSSSHRYKGVPS   60
h3-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVDNRVAWHQQKPGKAPKALIYSSSHRYKGVPS   60
f5-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVEDRVAWHQQKPGKAPKALIYSSSHRYKGVPS   60
e4b6g3c6h2c2d1a6c3a3e6d6g2-VL      DIQMTQSPSFLSASVGDRVTITCKASQNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
e3-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVGDRVAWHQQKPGKAPKALIYSSSHRYKGVPS   60
d5-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVEDKVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
d3f1g1-VL                          DIQMTQSPSFLSASVGDRVTITCKASQNVADRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
c4f4f2a2a1-VL                      DIQMTQSPSFLSASVGDRVTITCKASQNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
b5h4a4-VL                          DIQMTQSPSFLSASVGDRVTITCKASQNVDNRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
b2c5b3e2g4h6-VL                    DIQMTQSPSFLSASVGDRVTITCKASQNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
b1-VL                              DIQMTQSPSFLSASVGDRVTITCKASQNVGNRVAWYQQKPGKAPKALIYSSSHRYSGVPS   60
b4e1f3-VL                          DIQMTQSPSFLSASVGDRVTITCKASQNVGNRVAWYQQKPGKAPKALIYSSSHRYKGVPS   60
                                   ****************************** ::***:******************.****

a5-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
c1d2d4-VL                          RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
h3-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
f5-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
e4b6g3c6h2c2d1a6c3a3e6d6g2-VL      RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
e3-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
d5-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
d3f1g1-VL                          RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
c4f4f2a2a1-VL                      RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
b5h4a4-VL                          RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
b2c5b3e2g4h6-VL                    RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
b1-VL                              RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
b4e1f3-VL                          RFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK  107
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Consensus VL: SEQ ID NO: 230
DIQMTQSPSFLSASVGDRVTITCKASQNV G/E/A/D N/D R/K VAW Y/H QQKPGKAPKALIYSSSHRY K/S GVPSRFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK
Consensus VL: SEQ ID NO: 3289
DIQMTQSPSFLSASVGDRVTITCKASQNV$X_1X_2X_3$VAWX_4QQKPGKAPKALIYSSSHRYX_5 GVPSRFSGSGSGTEFTLTISSLQPEDFATYFCQQFKSYPLTFGQGTKLEIK, wherein X_1 is G, E, A or D; X_2 is N or D; X_3 is R or K; X_4 is Y or H; and X_5 is K or S

FIG. 35A

Alignment of affinity matured humanized Antibody A-H VH sequences (SEQ ID NOS 3390-3436, respectively, in order of appearance)

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A-H.52-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTLGYIHWVRQAPGQGLEWMGWFFPGSGNIKY  60
A-H.53-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFRLTYIHWVRQAPGQGLEWMGWFFPGSGNIKY  60
A-H.54-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFHNWYIHWVRQAPGQGLEWMGWFFPGSGNIKY  60
A-H.51-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFFPGSGNIKY  60
A-H.50-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGRIFPGSGNIKY  60
A-H.47-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFFPGSGNTKY  60
A-H.49-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFSPGSGNTKY  60
A-H.48-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFSPGSGNTKY  60
A-H.45-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFSAGSGNTKY  60
A-H.46-VH       QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLEWMGWFSAGSGNTKY  60
c2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTYIHWVRQAPGQGLEWMGRVYPGSGNTKY  60
f5-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTYIHWVRQAPGQGLEWMGRVSPGSGNTKY  60
f3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTYIHWVRQAPGQGLEWMGRISPGSGNTKY  60
e2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRISPGSGNTKY  60
e1-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
c1-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTYIHWVRQAPGQGLEWMGRVSPGSGNTKY  60
a1-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRVSPGSGNTKY  60
b3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRVSPGSGNVKY  60
h3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRISPGSGNVKY  60
c3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTYIHWVRQAPGQGLEWMGRIFPGSGNTKY  60
a5b5c4-VH       QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRIFPGSGNVKY  60
d6-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRIFPGSGNTKY  60
h2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGGTFKLTYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
c5-VH           QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
f2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRISAGSGNTKY  60
d3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFRLTYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
a4e4-VH         QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
d2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
g1-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTYIHWVRQAPGQGLEWMGRIYPGSGNVKY  60
c6-VH           QVQLVQSGAEVKKPGSSVKVSCKASGGTFDKTYIHWVRQAPGQGLEWMGRISAGSGNTKY  60
g2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKTYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
b4-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIYIHWVRQAPGQGLEWMGRVSAGSGNTKY  60
a6-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIYIHWVRQAPGQGLEWMGRIFAGSGNTKY  60
a2g4-VH         QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIYIHWVRQAPGQGLEWMGRISAGSGNVKY  60
b6f1-VH         QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIYIHWVRQAPGQGLEWMGRISAGSGNTKY  60
g3-VH           QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIYIHWVRQAPGQGLEWMGRISAGSGNIKY  60
d1-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFYIHWVRQAPGQGLEWMGRISAGSGNTKY  60
h4-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFYIHWVRQAPGQGLEWMGRVSAGSGNTKY  60
b2-VH           QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFYIHWVRQAPGQGLEWMGRIFAGSGNVKY  60
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FIG. 35B

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h6-VH                QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKFYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
b1-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
f4-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
a3-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFRDFYIHWVRQAPGQGLEWMGRVYPGSGSYRY  60
e6-VH                QVQLVQSGAEVKKPGSSVKVSCKASGTDFHLWYIHWVRQAPGQGLEWMGRVFAGSGSYRY  60
e3-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWYIHWVRQAPGQGLEWMGRISPGSGNVKY  60
d4-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWYIHWVRQAPGQGLEWMGRVSAGSGNVKY  60
d5-VH                QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWYIHWVRQAPGQGLEWMGRVFAGSGNTKY  60
                     ************************  *   ********************  . ***. :*

A-H.52-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
A-H.53-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
A-H.54-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
A-H.51-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSIYSAGVLDYWGQGTTVTVSS  119
A-H.50-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
A-H.47-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSIYSYDVLDYWGQGTTVTVSS  119
A-H.49-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSSYSYDVLDYWGQGTTVTVSS  119
A-H.48-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAVSYYSYDVLDYWGQGTTVTVSS  119
A-H.45-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAVSYYSYDVLDYWGQGTTVTVSS  119
A-H.46-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
c2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
f5-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
f3-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
e2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
e1-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
c1-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
a1-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
b3-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
h3-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
c3-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
a5b5c4-VH            NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
d6-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
h2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
c5-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
f2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
d3-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
a4e4-VH              NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
d2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
g1-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
c6-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
g2-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
b4-VH                NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS  119
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FIG. 35B (continued)

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a6-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
a2g4-VH        NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
b6f1-VH        NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
g3-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
d1-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
h4-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
b2-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
h6-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
b1-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
f4-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
a3-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
e6-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
e3-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
d4-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
d5-VH          NEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQGTTVTVSS   119
               ********************************** * ** .***************
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Consensus VH: SEQ ID NO: 231
QVQLVQSGAEVKKPGSSVKVSCKASG H/T/G/Y D/T/S F H/R/D/K/T L/D/K/T/N W/F/T/I/Y/G YIHWVRQAPGQGLEWMG R/W V/I/F F/S/Y A/P GSG N/S T/V/Y/I K/R YNEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYCA G/V S Y/I YS Y/A D/G VLDYWGQGTTVTVSS

Consensus VH: SEQ ID NO: 3290
QVQLVQSGAEVKKPGSSVKVSCKASG$X_1X_2FX_3X_4X_5$YIHWVRQAPGQGLEWMG$X_6X_7X_8X_9$GSG$X_{10}X_{11}X_{12}$YNEKFKGRVTIT ADTSTSTAYMELSSLRSEDTAVYYCA$X_{13}SX_{14}YSX_{15}X_{16}$VLDYWGQGTTVTVSS, wherein: X_1 is H or T or G or Y; X_2 is D or T or S; X_3 is H or R or D or K or T; X_4 is L or D or K or T or N; X_5 is W or F or T or I or Y or G; X_6 is R or W; X_7 is V or I or F; X_8 is F or S or Y; X_9 is A or P; X_{10} is N or S; X_{11} is T or V or Y or I; X_{12} is K or R; X_{13} is G or V; X_{14} is Y or I; X_{15} is Y or A; and X_{16} is D or G

FIG. 35B (continued)

ANTI-TCR ANTIBODY MOLECULES AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 17/256,917 filed on Dec. 29, 2020, which is a U.S. National Phase Application under 35 U.S.C. § 371 of International Application No. PCT/US2019/040592 filed on Jul. 3, 2019, which claims the benefit of U.S. Provisional Application 62/693,653 filed on Jul. 3, 2018, U.S. Provisional Application 62/737,829 filed on Sep. 27, 2018, U.S. Provisional Application 62/788,674 filed on Jan. 4, 2019, and U.S. Provisional Application 62/808,700 filed on Feb. 21, 2019, the entire contents of each of which are hereby incorporated by reference.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on Aug. 17, 2022, is named 53676_729_302 SL.xml and is 1,564,117 bytes in size.

BACKGROUND

Current molecules designed to redirect T cells to promote tumor cell lysis for cancer immunotherapy typically target the CD3 epsilon (CD3e) subunit of the T cell receptor (TCR). However, there are limitations to this approach. Previous studies have shown that, e.g., low doses of anti-CD3e monoclonal antibody (mAb) can cause T cell dysfunction and exert immunosuppressive effects. In addition, anti-CD3e mAbs bind to all T cells and thus activate a large number of T cells. Such non-physiological massive activation of T cells by these anti-CD3e mAbs can result in the production of proinflammatory cytokines such as IFN-gamma, IL-1-beta, IL-6, IL-10 and TNF-alpha, causing a "cytokine storm" known as the cytokine release syndrome (CRS), which is also associated with neurotoxicity (NT). Thus, it might be advantageous to develop antibodies that avoid or reduce CRS and/or NT.

SUMMARY OF THE INVENTION

Provided herein, in one aspect, is a method of expanding T cells that expresses a T cell receptor beta variable region (TCRβV) in a T cell population, the method comprising: contacting the T cell population with a composition comprising a multispecific molecule, wherein the multispecific molecule comprises a first domain that binds to a first target molecule and a second domain that binds to a second target molecule, wherein the first target molecule is a TCRβV and the second target molecule is a target molecule on a target cell that is different from the first target molecule, and wherein the first domain contacts the TCRβV of a T cell receptor (TCR) expressed by the T cells in the T cell population, thereby expanding the T cells in the T cell population.

In some embodiments, the T cell population is an in vivo T cell population.

In some embodiments, the second domain comprises a tumor-targeting domain, a cytokine molecule, or a stromal modifying domain.

In some embodiments, the multispecific molecule comprises at least two non-contiguous polypeptide chains, wherein a first polypeptide chain of the at least two non-contiguous polypeptide chains comprises a first member of a dimerization module, and a second polypeptide chain of the at least two non-contiguous polypeptide chains comprises a second member of the dimerization module, wherein the first polypeptide chain and the second polypeptide chain form a complex via the first member of the dimerization module and the second member of the dimerization module.

In some embodiments, the first polypeptide chain comprises the first domain and the second polypeptide chain comprises the second domain, wherein: (i) the first polypeptide chain comprises the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises the second domain linked to the second member of the dimerization module; (ii) the first polypeptide chain comprises a first portion of the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises a first portion of the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the first domain and a fourth polypeptide chain comprising a second portion of the second domain; (iii) the first polypeptide chain comprises a first portion of the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the first domain; or (iv) the first polypeptide chain comprises the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises a first portion of the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the second domain.

In some embodiments, the multispecific molecule further comprises a linker between the first domain and the first member of the dimerization module, a linker between the second domain and the second member of the dimerization module, a linker between the first portion of the first domain and the first member of the dimerization module, a linker between the first portion of the second domain and the second member of the dimerization module, a linker between the first member of the dimerization module and the second domain, a linker between the first member of the dimerization module and the first portion of the second domain or a combination thereof, wherein the linker is selected from a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non helical linker.

In some embodiments, the first polypeptide chain comprises the first domain and the second domain, wherein the first polypeptide chain comprises: (i) the first domain linked to the first member of the dimerization module linked to the second domain; (ii) a first portion of the first domain linked to the first member of the dimerization module linked to a first portion of the second domain, wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the first domain and a fourth polypeptide chain comprising a second portion of the second domain; (iii) a first portion of the first domain linked to the first member of the dimerization

module linked to the second domain, wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the first domain; or (iv) the first domain linked to the first member of the dimerization module linked to a first portion of the second domain, wherein the at least two non-contiguous polypeptide chains comprises a third polypeptide chain comprising a second portion of the second domain.

In some embodiments, the multispecific molecule further comprises a linker between the first domain and the first member of the dimerization module, a linker between the second domain and the second member of the dimerization module, a linker between the first portion of the first domain and the first member of the dimerization module, a linker between the first portion of the second domain and the second member of the dimerization module, a linker between the first member of the dimerization module and the second domain, a linker between the first member of the dimerization module and the first portion of the second domain or a combination thereof, wherein the linker is selected from a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non helical linker.

In some embodiments, the multispecific molecule comprises a polypeptide sequence comprising: (i) the first domain linked to the second domain; (ii) a first portion of the first domain linked to a first portion of the second domain, wherein the polypeptide sequence further comprises a second portion of the first domain and a second portion of the second domain; (iii) a first portion of the first domain linked to the second domain, wherein the polypeptide sequence further comprises a second portion of the first domain; or (iv) the first domain linked to a first portion of the second domain, wherein the polypeptide sequence further comprises a second portion of the second domain.

In some embodiments, the polypeptide sequence further comprises a linker between the first domain and the second domain, a linker between the first portion of the first domain and the first portion of the second domain, a linker between the first portion of the first domain and the second domain, a linker between the first domain and the first portion of the second domain, or a combination thereof, wherein the linker is selected from a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non-helical linker.

In some embodiments, the TCRβV is TCRβV1, TCRβV2, TCRβV3, TCRβV4, TCRβV5, TCRβV6, TCRβV7, TCRβV8, TCRβV9, TCRβV10, TCRβV11, TCRβV12, TCRβV19, TCRβV20, TCRβV21, TCRβV23, TCRβV24, TCRβV25, TCRβV26, TCRβV27, TCRβV28, TCRβV29 or TCRβV30.

In some embodiments, the TCRβV is TCRβV2, TCRβV4-1, TCRβV4-2, TCRβV5-1, TCRβV5-5, TCRβV5-6, TCRβV6, TCRβ6-5, TCRβV6-6, TCRβV6-9, TCRβV7-2, TCRβV7-3, TCRβV7-8, TCRβV7-9, TCRβV9, TCRβV10-1, TCRβV10-2, TCRβV10-3, TCRβV11-2, TCRβV12-3, TCRβV12-4, TCRβV12-5, TCRβV19, TCRβV20-1, TCRβV21, TCRβV24-1, TCRβV25-1 or TCRβV28.

In some embodiments, the TCRβV is TCRβV2, TCRβV3-1, TCRβV4-1, TCRβV4-2, TCRβV5-1, TCRβV5-4, TCRβV5-5, TCRβV5-6, TCRβV6-1, TCRβV6-5, TCRβV6-6, TCRβV7-3, TCRβV7-6, TCRβV7-8, TCRβV9, TCRβV11-2, TCRβV19, TCRβV20-1, TCRβV24-1, TCRβV27, TCRβV28, TCRβV29-1 or TCRβV30.

In some embodiments, the second target molecule is selected from the group consisting of BCMA, FcRH5, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD99, CD123, FcRH5, CLEC12, CD179A, SLAMF7, or NY-ESO1, PDL1, CD47, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PSMA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, MC1R, b-catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, MUC-1, CA-125, BAGE, GAGE, NY-ESO-1, b-catenin, CDK4, CDC27, a actinin-4, TRP1/gp75, TRP2, gplOO, Melan-A/MART1, gangliosides, WT1, EphA3, Epidermal growth factor receptor (EGFR), MART-2, MART-1, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RUI1, RUI2, SAGE, TRG, TRP1, TSTA, Folate receptor alpha, L1-CAM, CAIX, gpA33, GD3, GM2, VEGFR, Intergrin, a carbohydrates, IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, FAP, TGF-beta, hyaluronic acid, collagen, tenascin C and tenascin W.

In some embodiments, the second domain is an NK cell engager, a T cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager.

In some embodiments, the second domain is a T cell engager and wherein the second target molecule is a TCRβV other than the TCRβV to which the first domain binds.

In some embodiments, the second target molecule is not a TCRβV.

In some embodiments, the second target molecule is CD19.

In some embodiments, the second target molecule is CD3.

In some embodiments, the second target molecule is CD123.

In some embodiments, the second domain comprises a tumor-targeting domain and the second target molecule is a cancer antigen.

In some embodiments, the cancer antigen is a hematological cancer antigen, a solid tumor antigen, a metastatic cancer antigen, a soft tissue tumor antigen, a cancer antigen of a metastatic lesion or a stromal antigen.

In some embodiments, the cancer antigen is: (i) the solid tumor antigen, wherein the solid tumor is pancreatic cancer, breast cancer, colorectal cancer, lung cancer, skin cancer, ovarian cancer, or liver cancer; or (ii) the hematological cancer antigen, wherein the hematological cancer is a B-cell malignancy or a T cell malignancy.

In some embodiments, the cancer antigen is the hematological cancer antigen and the B-cell malignancy or the T cell malignancy is Hodgkin's lymphoma, Non-Hodgkin's lymphoma, acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, or acute lymphocytic leukemia.

In some embodiments, the cancer antigen is the hematological cancer antigen and the B-cell malignancy is Hodgkin's lymphoma, wherein the Non-Hodgkin's lymphoma is B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, or hairy cell leukemia.

In some embodiments, the second domain comprises a cytokine molecule selected from the group consisting of interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), interferon gamma and functional fragments or variants thereof.

In some embodiments, binding of the first domain to the TCRβV and binding of the second molecule to the target molecule promotes the T cells to kill cancer cells.

In some embodiments, the target cell is a T cell.

In some embodiments, the target cell is a non-cancer cell.

In some embodiments, the method expands T cells in vivo.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**A-**1**B shows the alignment of the Antibody A source mouse VH and VL framework 1, CDR 1, framework 2, CDR 2, framework 3, CDR3, and framework 4 regions with their respective humanized sequences. Kabat CDRs are shown in bold, Chothia CDRs are shown in italics, and combined CDRs are shown in boxes. The framework positions that were back mutated are double underlined. FIG. **1**A shows VH sequences for murine Antibody A (SEQ ID NO: 1) and humanized Antibody A-H (SEQ ID NO: 9). FIG. **1**B shows VL sequences for murine Antibody A (SEQ ID NO: 2) and humanized Antibody A-H (SEQ ID NO: 10 and SEQ ID NO: 11).

FIGS. **2**A-**2**B shows the alignment of the Antibody B source mouse VH and VL framework 1, CDR 1, framework 2, CDR 2, framework 3, CDR3, and framework 4 regions with their respective humanized sequences. Kabat CDRs are shown in bold, Chothia CDRs are shown in italics, and combined CDRs are shown in boxes. The framework positions that were back mutated are double underlined. FIG. **2**A shows the VH sequence for murine Antibody B (SEQ ID NO: 15) and humanized VH sequences B-H.1A to B-H.1C (SEQ ID NOs: 23-25). FIG. **2**B shows the VL sequence for murine Antibody B (SEQ ID NO: 16) and humanized VL sequences B-H.1D to B-H.1H (SEQ ID NOs: 26-30).

FIG. **3** depicts the phylogenetic tree of TCRBV gene family and subfamilies with corresponding antibodies mapped. Subfamily identities are as follows: Subfamily A: TCRβV6; Subfamily B: TCRβV10; Subfamily C: TCRβV12; Subfamily D: TCRβV5; Subfamily E: TCRβV7; Subfamily F: TCRβV11; Subfamily G: TCRβV14; Subfamily H: TCRβV16; Subfamily I: TCRβV18; Subfamily J: TCRβV9; Subfamily K: TCRβV13; Subfamily L: TCRβV4; Subfamily M: TCRβV3; Subfamily N: TCRβV2; Subfamily O: TCRβV15; Subfamily P: TCRβV30; Subfamily Q: TCRβV19; Subfamily R: TCRβV27; Subfamily S: TCRβV28; Subfamily T: TCRβV24; Subfamily U: TCRβV20; Subfamily V: TCRβV25; and Subfamily W: TCRβV29 subfamily. Subfamily members are described in detail herein in the Section titled "TCR beta V (TCRβV)".

FIGS. **4**A-**4**C show human CD3+ T cells activated by anti-TCR Vβ13.1 antibody (A-H.1) for 6-days. Human CD3+ T cells were isolated using magnetic-bead separation (negative selection) and activated with immobilized (plate-coated) anti-TCR Vβ13.1 (A-H.1) or anti-CD3∈ (OKT3) antibodies at 100 nM for 6 days. FIG. **4**A shows two scatter plots (left: activated with OKT3; and right: activated with A-H.1) of expanded T cells assessed for TCR Vβ13.1 surface expression using anti-TCR Vβ13.1 (A-H.1) followed by a secondary fluorochrome-conjugated antibody for flow cytometry analysis. FIG. **4**B shows percentage (%) of TCR Vβ13.1 positive T cells activated by anti-TCR Vβ13.1 (A-H.1) or anti-CD3e (OKT3) plotted against total T cells (CD3+). FIG. **4**C shows relative cell count acquired by counting the number of events in each T cell subset gate (CD3 or TCR Vβ13.1) for 20 seconds at a constant rate of 600/min. Data shown as mean value from 3 donors.

FIGS. **5**A-**5**B show cytolytic activity of human CD3+ T cells activated by anti-TCR Vβ13.1 antibody (A-H.1) against transformed cell line RPMI 8226. FIG. **5**A depicts target cell lysis of human CD3+ T cells activated with A-H.1 or OKT3. Human CD3+ T cells were isolated using magnetic-bead separation (negative selection) and activated with immobilized (plate-coated) A-H.1 or OKT3 at the indicated concentrations for 4 days prior to co-culture with RPMI 8226 cells at a (E:T) ratio of 5:1 for 2 days. Samples were next analyzed for cell lysis of RPMI 8226 cells by FACS staining for CFSE/CD138-labeled, and membrane-impermeable DNA dyes (DRAQ7) using flow cytometry analysis. FIG. **5**B shows target cell lysis of human CD3+ T cells activated with A-H.1 or OKT3 incubated with RPMI-8226 at a (E:T) ratio of 5:1 for 6 days followed by cell lysis analysis of RPMI 8226 cells as described above. Percentage (%) target cell lysis was determined by normalizing to basal target cell lysis (i.e. without antibody treatment) using the following formula, [(x−basal)/(100%−basal), where x is cell lysis of sample]. Data shown is a representative of n=1 donor.

FIGS. **6**A-**6**B show IFNg production by human PBMCs activated with the indicated antibodies. Human PBMCs were isolated from whole blood from the indicated number of donors, followed by solid-phase (plate-coated) stimulation with the indicated antibodies at 100 Nm. Supernatant was collected on Days 1, 2, 3, 5, or 6. FIG. **6**A is a graph comparing the production of IFNg in human PBMCs activated with the antibodies indicated activated with anti-TCR Vβ13.1 antibodies (A-H.1 or A-H.2) or anti-CD3e antibodies (OKT3 or SP34-2) on Day 1, 2, 3, 5, or 6 post-activation. FIG. **6**B shows IFNg production in human PBMCs activated with the antibodies indicated activated with the indicated anti-TCR Vβ13.1 antibodies or anti-CD3e antibody (OKT3) on Day 1, 2, 3, 5, or 6 post-activation.

FIGS. **7**A-**7**B show IL-2 production by human PBMCs activated with the indicated antibodies. A similar experimental setup as described for FIGS. **6**A-**6**B was used.

FIGS. **8**A-**8**B show IL-6 production by human PBMCs activated with the indicated antibodies. A similar experimental setup as described for FIGS. **6**A-**6**B was used.

FIGS. **9**A-**9**B show TNF-alpha production by human PBMCs activated with the indicated antibodies. A similar experimental setup as described for FIGS. **6**A-**6**B was used.

FIGS. **10**A-**10**B show IL-1beta production by human PBMCs activated with the indicated antibodies. A similar experimental setup as described for FIGS. **6**A-**6**B was used.

FIGS. **11**A-**11**B are graphs showing delayed kinetics of IFNg secretion in human PMBCs activated by anti-TCR Vβ13.1 antibody A-H.1 when compared to PBMCs acti-

vated by anti-CD3e antibody OKT3. FIG. **11**A shows IFNg secretion data from 4 donors. FIG. **11**B shows IFNg secretion data from 4 additional donors. Data shown is representative of n=8 donors.

FIG. **12** depicts increased CD8+ TSCM and Temra T cell subsets in human PBMCs activated by anti-TCR Vβ13.1 antibodies (A-H.1 or A-H.2) compared to PBMCs activated by anti-CD3e antibodies (OKT3 or SP34-2).

FIGS. **13**A-**13**F show characterization of an anti-TCRVb antibody. FIG. **13**A is a graph depicting proliferation of T cells activated with anti-CD3 (OKT3) antibody or anti-TCRVb antibody. FIG. **13**B shows selective expansion of CD45RA+ effector memory CD8+ and CD4+ T cells (TEMRA) cells with anti-TCRVb antibodies. Tn=naïve T cell; Tscm=stem cell memory T cell; Tcm=central memory T cell; Tem=effector memory T cell; Temra=effector memory CD45RA+ T cell. FIG. **13**C is a graph showing IFN-g secretion by PBMCs stimulated with an anti-TCRVb antibody, or anti-CD3 antibodies. FIG. **13**D shows target cell lysis by T cells stimulated with an anti-TCRVb antibody, or anti-CD3 antibodies. Cells were stimulated for 4 days followed by 2 days incubation with multiple myeloma target cells for assessment of cell killing. FIG. **13**E is a graph showing perforin secretion by T cells stimulated with an anti-TCRVb antibody, or an anti-CD3 antibody. Perforin was analyzed by FACS staining in TCRVB-positive and TCRVB-negative T cells in PBMCs after 5 days of stimulation with 100 ng/ml plate-bound antibody. FIG. **13**F is a graph showing Granzyme B by T cells stimulated with an anti-TCRVb antibody, or an anti-CD3 antibody. Granzyme B was analyzed by FACS staining in TCRVB-positive and TCRVB-negative T cells in PBMCs after 5 days of stimulation with 100 ng/ml plate-bound antibody.

FIGS. **14**A-**14**B show production of IL-2 and IL-15 and expansion of human NK cells by stimulation of PBMCs with anti-TCRVb antibody for 6 days at a dose of 100 nM. FIG. **14**A shows secretion of IL-2 or IL-15 in T cells stimulated with an anti-TCRVb antibody, or anti-CD3 antibodies. FIG. **14**B depicts flow cytometry dot plots showing NKp46 staining vs CD56 antibody staining in cells stimulated with an anti-TCRVb antibody or an anti-CD3 antibody or a control sample.

FIGS. **15**A-**15**C show secretion of cytokines in PBMCs stimulated with an anti-TCRVb antibody, or anti-CD3 antibodies.

FIGS. **16**A-**16**B show killing of MM cells by dual targeting BCMA-TCRvb antibody molecules. FIG. **16**A shows in vitro killing by one of the following dual-targeting antibody molecules: BCMA-TCRVb (Molecule I), BCMA-CD3, or Control-TCRVb; or an isotype control. FIG. **16**B shows in vivo killing of MM cells by a dual-targeting BCM-TCRVb antibody (Molecule I).

FIG. **17** shows lysis of MM target cells with a dual targeting antibody (Molecule E) which recognized FcRH5 on one arm and TCRVb on the other arm.

FIGS. **18**A-**18**B demonstrate cytokine production from human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) when compared to those activated by anti-CD3E antibodies (OKT3 or SP34-2). FIG. **18**A shows that human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) produce similar or reduced levels of IFNγ. FIG. **18**B shows human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) produce higher levels of IL-2 when compared to those activated by anti-CD3∈ antibodies (OKT3 or SP34-2). Data shown is representative of n=6 donors.

FIGS. **19**A-**19**C demonstrate cytokine production from human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1). Human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) do not significantly produce IL-6 (FIG. **19**A), IL1b (FIG. **19**B), and less TNFa (FIG. **19**C), when compared to PBMCs activated by anti-CD3∈ antibodies (OKT3 or SP34-2). Data shown is representative of n=6 donors.

FIGS. **20**A-**20**E demonstrate cytokine production from human PBMCs activated by anti-TCRβV Antibody D antibody compared to control anti-CD3e antibody (OKT3). FIG. **20**A shows that human PBMCs activated by anti-TCRβV Antibody D antibody produce similar or reduced levels of IFNγ. FIG. **20**B shows human PBMCs activated by anti-TCRβV Antibody D antibody produce higher levels of IL-2 when compared to those activated by anti-CD3∈ antibodies (OKT3). Human PBMCs activated by anti-TCRβV Antibody D antibody do not significantly produce IL-1beta (FIG. **20**C), IL-6, (FIG. **20**D), or TNFalpha (FIG. **20**E). Data shown is representative of n=4 donors.

FIGS. **21**A-**21**B demonstrate cytokine production from human PBMCs activated by anti-TCR Vβ5 antibody (Antibody E). FIG. **21**A shows that human PBMCs activated by anti-TCR Vβ5 antibody produce similar or reduced levels of IFNγ compared to PBMCS activated by anti-CD3∈ antibodies (OKT3 or SP34-2). FIG. **21**B shows human PBMCs activated by the anti-TCR Vβ5 1 antibody produce higher levels of IL-2 when compared to those activated by anti-CD3∈ antibodies (OKT3 or SP34-2). Data shown is representative of n=4 donors.

FIGS. **22**A-**22**D demonstrate cytokine production from human PBMCs activated by an anti-TCR Vβ5 antibody (Antibody E). Human PBMCs activated by anti-TCR Vβ5 antibody do not significantly produce IL-1beta (FIG. **22**A), IL-6, (FIG. **22**B), TNFalpha (FIG. **22**C), or IL-10 (FIG. **22**D) as compared to PBMCs activated by anti-CD3∈ antibodies (OKT3 or SP34-2). Data shown is representative of n=4 donors.

FIGS. **23**A-**23**F demonstrate cytokine production from human PBMCs activated by a dual targeting (bispecific molecule) comprising an anti-TCRβV binding moiety and a BCMA binding moiety. FIG. **23**A shows that human PBMCs activated by the bispecific molecule produce similar or reduced levels of IFNγ as PBMCS activated by anti-CD3∈ antibodies (OKT3). FIG. **23**B shows human PBMCs activated by the bispecific molecule produce higher levels of IL-2 when compared to PBMCs activated by anti-CD3E antibodies (OKT3). Human PBMCs activated by the bispecific molecule do not significantly produce IL-1beta (FIG. **23**C), IL-6, (FIG. **23**D), TNFalpha (FIG. **23**E), or IL-10 (FIG. **23**F). Data shown is representative of n=3 donors.

FIGS. **24**A-**24**B show the structure and sequence of eight TCRβV proteins from seven different subfamilies: TCRβV6 subfamily (TCRβV6-5 and TCRβV6-4 are shown), TCRβV28 subfamily, TCRβV19 subfamily, TCRβV9 subfamily, TCRβV5 subfamily, TCRβV20 subfamily and TCRβV12 subfamily. FIG. **24**A shows the structural alignment of the different TCRβV proteins. The circled area represents the outward facing region comprising the proposed binding site for the anti-TCRβV antibodies disclosed herein. FIG. **24**B shows the amino acid sequence alignment of the proteins shown in FIG. **24**A (SEQ ID NOS 3449-3456, respectively, in order of appearance). The various TCRβV proteins (from 7 different TCRβV subfamilies) have diverse sequences but share a conserved (similar) structure and function.

FIGS. **25**A-**25**J show cytokine or chemokine secretion of PBMCs activated with anti-TCRVb antibodies (A-H.1, B-H.1), a bispecific molecule comprising an anti-TCRVb

antibody (Molecule H), control isotype (122) or anti-CD3e antibody (OKT3). Data shown is representative of n=2 donors and representative of 2 independent experiments.

FIGS. **26**A-**26**H show cytokine or chemokine secretion of PBMCs activated with anti-TCRVb antibodies (A-H.1, B-H.1), a bispecific molecule comprising an anti-TCRVb antibody (Molecule H), control isotype (122) or anti-CD3e antibody (OKT3). Data shown is representative of n=2 donors and representative of 2 independent experiments.

FIGS. **27**A-**27**L show cytokine or chemokine secretion of PBMCs activated with anti-TCRVb antibodies (A-H.1, B-H.1), a bispecific molecule comprising an anti-TCRVb antibody (Molecule H), control isotype (122) or anti-CD3e antibody (OKT3). Data shown is representative of n=2 donors and representative of 2 independent experiments.

FIG. **28** is a graph depicting mean tumor volume in NOD/SCID/IL-2Rγnull (NSG) mice engrafted with Raji-luc cells at days 10 to 28. The Star denotes PBMC implantation. Open triangles denote antibody treatment with the indicated antibodies.

FIGS. **29**A-**29**B depicting Mean tumor burden (Total Flux) in NOD/SCID/IL-2Rγnull (NSG) mice engrafted with cancer cells and treated with the indicated antibody. NSG mice were implanted with PBMCs on Day 1 followed by injection with cancer cells on Day 7 (Raji-luc in FIG. **29**A; K562-Luc control in FIG. **29**B). Antibody treatment with the indicated antibodies began on Day 16. FIG. **29**A shows mean tumor burden at days 16 to 37 in NOD/SCID/IL-2Rγnull (NSG) mice engrafted with Raji-luc cells. FIG. **29**B shows mean tumor burden (Total Flux) at days 16 to 30 in animals engrafted with K562-luc cells.

FIG. **30** is a graph depicting Mean tumor burden (Total Flux) mean tumor volume in NOD/SCID/IL-2Rγnull (NSG) mice engrafted with RPMI-8226 cells. The RPMI-8226 cells were engrafted on Day 1. On Day 11, PBMCs were implanted into the mice and antibody treatment began on Day 17.

FIGS. **31**A-**31**B are graphs showing % target cell lysis at different antibody concentrations. FIG. **31**A shows data generated using anti-TCR Vβ13.1/anti-CD19 (Molecule F), anti-CD3/anti-CD19, and anti-TCR Vβ13.1 (A-H.1). FIG. **31**B shows data generated using anti-TCR Vβ13.1/anti-BCMA (Molecule G), anti-CD3/anti-BCMA, and anti-TCR Vβ13.1 (A-H.1).

FIGS. **32**A-**32**F are graphs showing cytokine secretion stimulated by anti-TCR Vβ/anti-BCMA (Molecule H) or anti-CD3 (OKT3) at Days 1, 2, 3, and 5. Cytokines examined include: IFNγ, IL-2, IL-‖3, IL-6, IL-10, and TNFα (FIGS. **32**A-**32**F, respectively).

FIGS. **33**A-**33**F are graphs showing cytokine secretion stimulated by anti-TRBC1 (Antibody F) or anti-CD3 (OKT3) at Days 2 and 5. Cytokines examined include: IFNγ, IL-2, IL-1β, IL-6, IL-10, and TNFα (FIGS. **33**A-**33**F, respectively).

FIG. **34** is Table 9 showing alignment of TCRBV amino acid sequences (SEQ ID NOS 3457-3639, respectively, in order of appearance). The alignment of TCRBV amino acid sequences in Table 9 underscores the diversity of TCR sequences. In particular, the TRBV sequences from different subfamilies are considerably different from each other.

FIGS. **35**A and **35**B show alignment of affinity matured humanized Antibody A-H VL sequences (SEQ ID NOS 3377-3389, respectively, in order of appearance) (FIG. **35**A) and alignment of affinity matured humanized Antibody A-H VH sequences (SEQ ID NOS 3390-3436, respectively, in order of appearance) (FIG. **35**B), respectively.

DETAILED DESCRIPTION OF THE INVENTION

Current bispecific constructs designed to redirect T cells to promote tumor cell lysis for cancer immunotherapy typically utilize antibody fragments (Fab, scFv, VH, etc.) that are derived from monoclonal antibodies (mAb) directed against the CD3e subunit of the T cell receptor (TCR). However, there are limitations to this approach which may prevent the full realization of the therapeutic potential for such bispecific constructs. Previous studies have shown that even low "activating" doses of anti-CD3e mAb can cause long-term T cell dysfunction and exert immunosuppressive effects. In addition, anti-CD3e mAbs have been associated with side effects that result from massive T cell activation. The large number of activated T cells secrete substantial amounts of cytokines, the most important of which is Interferon gamma (IFNg). This excess amount of IFNg in turn activates macrophages which then overproduce proinflammatory cytokines such as IL-1beta, IL-6, IL-10 and TNF-alpha, causing a "cytokine storm" known as the cytokine release syndrome (CRS) (Shimabukuro-Vornhagen et al., J Immunother Cancer. 2018 Jun. 15; 6(1):56, herein incorporated by reference in its entirety). Thus, the need exists for developing antibodies that are capable of binding and activating only a subset of effector T cells, e.g., to reduce the CRS and/or neurotoxicity (NT).

This invention features molecules targeting the TCRβV chain of TCR and methods thereof. Without wishing to be bound by theory, such molecules are capable of binding, activating, and/or expanding only a subset of T cells, avoiding or reducing CRS and/or NT and minimizing potential immunosuppressive effects of anti-CD3 mAbs.

TCR is a disulfide-linked membrane-anchored heterodimeric protein normally consisting of the highly variable alpha (α) and beta (β) chains expressed as part of a complex with the invariant CD3 chain molecules. TCR on αβ T cells is formed by a heterodimer of one alpha chain and one beta chain. Each alpha or beta chain consists of a constant domain and a highly variable domain classified as the Immunoglobulin superfamily (IgSF) fold. The TCRβV chains can be further classified into 30 subfamilies (TRBV1-30). Despite their high structural and functional homology, the amino acid sequence homology in the TRBV genes is very low. Only 4 amino acids out of ~95 are identical while 10 additional amino acids are conserved among all subfamilies (see an alignment of TCRBV amino acid sequences in Table 9). Nevertheless, TCRs formed between alpha and beta chains of highly diverse sequences show a remarkable structural homology (FIGS. **24**A and **24**B) and elicit a similar function, e.g., activation of T cells.

Disclosed herein is the discovery of a novel class of antibodies, i.e., anti-TCRβV antibody molecules disclosed herein, which despite having low sequence similarity (e.g., low sequence identity among the different antibody molecules that recognize different TCRβV subfamilies), recognize a structurally conserved, yet sequence-wise variable, region, e.g., domain, on the TCRβV protein (as denoted by the circled area in FIG. **24**A) and have a similar function (e.g., activation of T cells and a similar cytokine profile as described herein). Thus, the anti-TCRβV antibody molecules disclosed herein share a structure-function relationship.

Without wishing to be bound by theory, it is believed that in some embodiments, the anti-TCRβV antibody molecules disclosed herein bind to an outward facing epitope of a TCRβV protein when it is in a complex with a TCRalpha protein, e.g., as denoted by the circled area in FIG. **24**A. In some embodiments, the anti-TCRβV antibody molecules disclosed herein recognize (e.g., bind to), a domain (e.g., an epitope) on the TCRβV protein that is: (1) structurally conserved among different TCRβV subfamilies; and (2) has minimal sequence identity among the different TCRβV subfamilies. As shown in Table 9, TCRβV proteins from the different TCRβV subfamilies share minimal sequence similarity. However, as shown in FIG. **24**A-B, TCRβV proteins which have minimal sequence similarity, share a similar 3D conformation and structure.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, an interface of a TCRβV:TCRalpha complex.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, a constant region of a TCRβV protein.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, one or more (e.g., all) of a complementarity determining region (e.g., CDR1, CDR2 and/or CDR3) of a TCRβV protein.

This disclosure provides, inter alia, antibody molecules directed to the variable chain of the beta subunit of TCR (TCRβV) which bind and, e.g., activate a subset of T cells. The anti-TCRβV antibody molecules disclosed herein result in lesser or no production of cytokines associated with CRS, e.g., IL-6, IL-1beta, IL-10 and TNF alpha; and enhanced and/or delayed production of IL-2 and IFNg. In some embodiments, the anti-TCRβV antibodies disclosed herein have a cytokine profile, e.g., as described herein, which differs from a cytokine profile of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager"). In some embodiments, the anti-TCRβV antibodies disclosed herein result in expansion of TCRβV+ T cells, e.g., a subset of memory effector T cells known as T_{EMRA}. Without wishing to be bound by theory, it is believed that in some embodiments, T_{EMRA} cells can promote tumor cell lysis but not CRS. Accordingly, provided herein are methods of making said anti-TCRβV antibody molecules and uses thereof. Also disclosed herein are multispecific molecules, e.g., bispecific molecules comprising said anti-TCRβV antibody molecules. In some embodiments, compositions comprising anti-TCRβV antibody molecules of the present disclosure, can be used, e.g., to: (1) activate and redirect T cells to promote tumor cell lysis for cancer immunotherapy; and/or (2) expand TCRβV+ T cells. In some embodiments, compositions comprising anti-TCRβV antibody molecules as disclosed herein limit the harmful side-effects of CRS and/or NT, e.g., CRS and/or NT associated with anti-CD3e targeting.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV12, or binds to TCRβV12 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV12 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV12 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule does not comprise the CDRs of the Antibody B murine antibody.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01, or binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV5-5*01 or TCRβV5-1*01 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule does not comprise the CDRs of the TM23 murine antibody.

Accordingly, provided herein are, inter alia, anti-TCRβV antibody molecules, multispecific or multifunctional molecules (e.g., multispecific or multifunctional antibody molecules) that comprise anti-TCRβV antibody molecules, nucleic acids encoding the same, methods of producing the aforesaid molecules, pharmaceutical compositions comprising aforesaid molecules, and methods of treating a disease or disorder, e.g., cancer, using the aforesaid molecules. The antibody molecules and pharmaceutical compositions disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose disorders and conditions, e.g., cancer, e.g., as described herein.

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention pertains.

The term "a" and "an" refers to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "about" when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of ±20% or in some instances ±10%, or in some instances ±5%, or in some instances ±1%, or in some instances ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods.

The term "acquire" or "acquiring" as the terms are used herein, refer to obtaining possession of a physical entity (e.g., a sample, a polypeptide, a nucleic acid, or a sequence), or a value, e.g., a numerical value, by "directly acquiring" or "indirectly acquiring" the physical entity or value. "Directly acquiring" means performing a process (e.g., performing a synthetic or analytical method) to obtain the physical entity or value. "Indirectly acquiring" refers to receiving the physical entity or value from another party or source (e.g., a third party laboratory that directly acquired the physical entity or value). Directly acquiring a physical entity includes performing a process that includes a physical change in a physical substance, e.g., a starting material. Directly acquiring a value includes performing a process that includes a physical change in a sample or another substance, e.g., performing an analytical process which includes a physical change in a substance, e.g., a sample.

As used herein, the term "T cell receptor beta variable chain" or "TCRβV," refers to an extracellular region of the T cell receptor beta chain which comprises the antigen recognition domain of the T cell receptor. The term TCRβV includes isoforms, mammalian, e.g., human TCRβV, species homologs of human and analogs comprising at least one common epitope with TCRβV. Human TCRβV comprises a gene family comprising subfamilies including, but not limited to: a TCRβV6 subfamily, a TCRβV10 subfamily, a TCRβV12 subfamily, a TCRβV5 subfamily, a TCRβV7 subfamily, a TCRβV11 subfamily, a TCRβV14 subfamily, a TCRβV16 subfamily, a TCRβV18 subfamily, a TCRβV9 subfamily, a TCRβV13 subfamily, a TCRβV4 subfamily, a TCRβV3 subfamily, a TCRβV2 subfamily, a TCRβV15 subfamily, a TCRβV30 subfamily, a TCRβV19 subfamily, a TCRβV27 subfamily, a TCRβV28 subfamily, a TCRβV24 subfamily, a TCRβV20 subfamily, TCRβV25 subfamily, a TCRβV29 subfamily, a TCRβV1 subfamily, a TCRβV17 subfamily, a TCRβV21 subfamily, a TCRβV23 subfamily, or a TCRβV26 subfamily, as well as family members of said subfamilies, and variants thereof (e.g., a structural or functional variant thereof). In some embodiments, the TCRβV6 subfamily comprises: TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, TCRβV comprises TCRβV6-5*01, or a variant thereof, e.g., a variant having 85%, 90%, 95%, 99% or more identity the naturally-occurring sequence. TCRβV6-5*01 is also known as TRBV65; TCRβV6S5; TCRβV13S1, or TCRβV13.1. The amino acid sequence of TCRβV6-5*01, e.g., human TCRβV6-5*01, is known in that art, e.g., as provided by IMGT ID L36092. In some embodiments, TCRβV6-5*01 is encoded by the nucleic acid sequence of SEQ ID NO: 43, or a sequence having 85%, 90%, 95%, 99% or more identity thereof. In some embodiments, TCRβV6-5*01 comprises the amino acid sequence of SEQ ID NO: 44, or a sequence having 85%, 90%, 95%, 99% or more identity thereof.

The term "human-like antibody molecule" as used herein refers to a humanized antibody molecule, human antibody molecule or an antibody molecule having at least 95% identity with a non-murine germline framework region, e.g., FR1, FR2, FR3 and/or FR4. In some embodiments, the human-like antibody molecule comprises a framework region having at least 95% identity to a human germline framework region, e.g., a FR1, FR2, FR3 and/or FR4 of a human germline framework region. In some embodiments, the human-like antibody molecule is a recombinant antibody. In some embodiments, the human-like antibody molecule is a humanized antibody molecule. In some embodiments, the human-like antibody molecule is human antibody molecule. In some embodiments, the human-like antibody molecule is a phage display or a yeast display antibody molecule. In some embodiments, the human-like antibody molecule is a chimeric antibody molecule. In some embodiments, the human-like antibody molecule is a CDR grafted antibody molecule.

The term "cytokine profile" as used herein, refers to the level and/or activity of on one or more cytokines or chemokines, e.g., as described herein. In some embodiments, a cytokine profile comprises the level and/or activity of a naturally occurring cytokine, a fragment or a variant thereof. In an embodiment, a cytokine profile comprises the level and/or activity of one or more cytokines and/or one or more chemokines (e.g., as described herein). In some embodiments, a cytokine profile comprises the level and/or activity of a naturally occurring cytokine, a fragment or a variant thereof. In some embodiments, a cytokine profile comprises the level and/or activity of a naturally occurring chemokine, a fragment or a variant thereof. In an embodiment, a cytokine profile comprises the level and/or activity of one or more of: IL-2 (e.g., full length, a variant, or a fragment thereof); IL-1beta (e.g., full length, a variant, or a fragment thereof); IL-6 (e.g., full length, a variant, or a fragment thereof); TNFα (e.g., full length, a variant, or a fragment thereof); IFNg (e.g., full length, a variant, or a fragment thereof) IL-10 (e.g., full length, a variant, or a fragment thereof); IL-4 (e.g., full length, a variant, or a fragment thereof); TNF alpha (e.g., full length, a variant, or a fragment thereof); IL-12p70 (e.g., full length, a variant, or a fragment thereof); IL-13 (e.g., full length, a variant, or a fragment thereof); IL-8 (e.g., full length, a variant, or a fragment thereof); Eotaxin (e.g., full length, a variant, or a fragment thereof); Eotaxin-3 (e.g., full length, a variant, or a fragment thereof); IL-8 (HA) (e.g., full length, a variant, or a fragment thereof); IP-10 (e.g., full length, a variant, or a fragment thereof); MCP-1 (e.g., full length, a variant, or a fragment thereof); MCP-4 (e.g., full length, a variant, or a fragment thereof); MDC (e.g., full length, a variant, or a fragment thereof); MIP-1a (e.g., full length, a variant, or a fragment thereof); MIP-1b (e.g., full length, a variant, or a fragment thereof); TARC (e.g., full length, a variant, or a fragment thereof); GM-CSF (e.g., full length, a variant, or a fragment thereof); IL-12 23p40 (e.g., full length, a variant, or a fragment thereof); IL-15 (e.g., full length, a variant, or a fragment thereof); IL-16 (e.g., full length, a variant, or a fragment thereof); IL-17a (e.g., full length, a variant, or a fragment thereof); IL-1a (e.g., full length, a variant, or a fragment thereof); IL-5 (e.g., full length, a variant, or a fragment thereof); IL-7 (e.g., full length, a variant, or a fragment thereof); TNF-beta (e.g., full length, a variant, or a fragment thereof); or VEGF (e.g., full length, a variant, or a fragment thereof). In some embodiments, a cytokine profile includes secretion of one or more cytokines or chemokines.

In an embodiment, a cytokine in a cytokine profile can be modulated, e.g., increased or decreased, by an anti-TCRBV antibody molecule described herein. In one embodiment, the cytokine profile includes cytokines associated with a cytokine storm or cytokine release syndrome (CRS), e.g., IL-6, IL-1beta, TNFalpha and IL-10.

The term "variant" refers to a polypeptide that has a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence. In some embodiments, the variant is a functional variant. In some embodiments, a TCRβV variant can bind to TCRα and form a TCR α:β complex.

The term "functional variant" refers to a polypeptide that has a substantially identical amino acid sequence to the naturally-occurring sequence, or are encoded by a substantially identical nucleotide sequence, and are capable of having one or more activities of the naturally-occurring sequence.

As used herein, a "multifunctional" or a "multispecific" molecule refers to molecule, e.g., a polypeptide, that has two or more functionalities, e.g., two or more binding specificities. In some embodiments, the functionalities can include one or more immune cell engagers, one or more tumor binding molecules, one or more cytokine molecules, one or more stromal modifiers, and other moieties described herein. In some embodiments, the multispecific molecule is a multispecific antibody molecule, e.g., a bispecific antibody molecule. In some embodiments, the multispecific molecule includes an anti-TCRVb antibody molecule as described herein.

In some embodiments, the multifunctional molecule includes an immune cell engager. "An immune cell engager" refers to one or more binding specificities that bind and/or activate an immune cell, e.g., a cell involved in an immune response. In embodiments, the immune cell is chosen from a T cell, an NK cell, a B cell, a dendritic cell, and/or the macrophage cell. The immune cell engager can be an antibody molecule, a receptor molecule (e.g., a full length receptor, receptor fragment, or fusion thereof (e.g., a receptor-Fc fusion)), or a ligand molecule (e.g., a full length ligand, ligand fragment, or fusion thereof (e.g., a ligand-Fc fusion)) that binds to the immune cell antigen (e.g., the T cell, the NK cell antigen, the B cell antigen, the dendritic cell antigen, and/or the macrophage cell antigen). In embodiments, the immune cell engager specifically binds to the target immune cell, e.g., binds preferentially to the target immune cell. For example, when the immune cell engager is an antibody molecule, it binds to an immune cell antigen (e.g., a T cell antigen, an NK cell antigen, a B cell antigen, a dendritic cell antigen, and/or a macrophage cell antigen) with a dissociation constant of less than about 10 nM.

In some embodiments, the multifunctional molecule includes a cytokine molecule. As used herein, a "cytokine molecule" refers to full length, a fragment or a variant of a cytokine; a cytokine further comprising a receptor domain, e.g., a cytokine receptor dimerizing domain; or an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor, that elicits at least one activity of a naturally-occurring cytokine. In some embodiments the cytokine molecule is chosen from interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-10 (IL-10), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), or interferon gamma, or a fragment or variant thereof, or a combination of any of the aforesaid cytokines. The cytokine molecule can be a monomer or a dimer. In embodiments, the cytokine molecule can further include a cytokine receptor dimerizing domain. In other embodiments, the cytokine molecule is an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor chosen from an IL-15Ra or IL-21R.

As used herein, the term "molecule" as used in, e.g., antibody molecule, cytokine molecule, receptor molecule, includes full-length, naturally-occurring molecules, as well as variants, e.g., functional variants (e.g., truncations, fragments, mutated (e.g., substantially similar sequences) or derivatized form thereof), so long as at least one function and/or activity of the unmodified (e.g., naturally-occurring) molecule remains.

In some embodiments, the multifunctional molecule includes a stromal modifying moiety. A "stromal modifying moiety," as used herein refers to an agent, e.g., a protein (e.g., an enzyme), that is capable of altering, e.g., degrading a component of, the stroma. In embodiments, the component of the stroma is chosen from, e.g., an ECM component, e.g., a glycosaminoglycan, e.g., hyaluronan (also known as hyaluronic acid or HA), chondroitin sulfate, chondroitin, dermatan sulfate, heparin sulfate, heparin, entactin, tenascin, aggrecan and keratin sulfate; or an extracellular protein, e.g., collagen, laminin, elastin, fibrinogen, fibronectin, and vitronectin.

Certain terms are defined below.

As used herein, the articles "a" and "an" refer to one or more than one, e.g., to at least one, of the grammatical object of the article. The use of the words "a" or "an" when used in conjunction with the term "comprising" herein may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

As used herein, "about" and "approximately" generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Exemplary degrees of error are within 20 percent (%), typically, within 10%, and more typically, within 5% of a given range of values.

"Antibody molecule" as used herein refers to a protein, e.g., an immunoglobulin chain or fragment thereof, comprising at least one immunoglobulin variable domain structure and/or sequence. An antibody molecule encompasses antibodies (e.g., full-length antibodies) and antibody fragments. In an embodiment, an antibody molecule comprises an antigen binding or functional fragment of a full length antibody, or a full length immunoglobulin chain. For example, a full-length antibody is an immunoglobulin (Ig) molecule (e.g., an IgG antibody) that is naturally occurring or formed by normal immunoglobulin gene fragment recombinatorial processes). In embodiments, an antibody molecule refers to an immunologically active, antigen-binding portion of an immunoglobulin molecule, such as an antibody fragment. An antibody fragment, e.g., functional fragment, is a portion of an antibody, e.g., Fab, Fab', $F(ab')_2$, $F(ab)_2$, variable fragment (Fv), domain antibody (dAb), or single chain variable fragment (scFv). A functional antibody fragment binds to the same antigen as that recognized by the intact (e.g., full-length) antibody. The terms "antibody fragment" or "functional fragment" also include isolated fragments consisting of the variable regions, such as the "Fv" fragments consisting of the variable regions of the heavy and light chains or recombinant single chain polypeptide molecules in which light and heavy variable regions are connected by a peptide linker ("scFv proteins"). In some embodiments, an antibody fragment does not include portions of antibodies without antigen binding activity, such as Fc fragments or single amino acid residues. Exemplary antibody molecules include full length antibodies and antibody fragments, e.g., dAb (domain antibody), single chain, Fab, Fab', and $F(ab')_2$ fragments, and single chain variable fragments (scFvs). In some embodiments, the antibody molecule is an antibody mimetic. In some embodiments, the antibody molecule is, or comprises, an antibody-like framework or scaffold, such as, fibronectins, ankyrin repeats (e.g.,

designed ankyrin repeat proteins (DARPins)), avimers, affibody affinity ligands, anticalins, or affilin molecules.

As used herein, an "immunoglobulin variable domain sequence" refers to an amino acid sequence which can form the structure of an immunoglobulin variable domain. For example, the sequence may include all or part of the amino acid sequence of a naturally-occurring variable domain. For example, the sequence may or may not include one, two, or more N- or C-terminal amino acids, or may include other alterations that are compatible with formation of the protein structure.

In embodiments, an antibody molecule is monospecific, e.g., it comprises binding specificity for a single epitope. In some embodiments, an antibody molecule is multispecific, e.g., it comprises a plurality of immunoglobulin variable domain sequences, where a first immunoglobulin variable domain sequence has binding specificity for a first epitope and a second immunoglobulin variable domain sequence has binding specificity for a second epitope. In some embodiments, an antibody molecule is a bispecific antibody molecule. "Bispecific antibody molecule" as used herein refers to an antibody molecule that has specificity for more than one (e.g., two, three, four, or more) epitope and/or antigen.

"Antigen" (Ag) as used herein refers to a molecule that can provoke an immune response, e.g., involving activation of certain immune cells and/or antibody generation. Any macromolecule, including almost all proteins or peptides, can be an antigen. Antigens can also be derived from genomic recombinant or DNA. For example, any DNA comprising a nucleotide sequence or a partial nucleotide sequence that encodes a protein capable of eliciting an immune response encodes an "antigen." In embodiments, an antigen does not need to be encoded solely by a full length nucleotide sequence of a gene, nor does an antigen need to be encoded by a gene at all. In embodiments, an antigen can be synthesized or can be derived from a biological sample, e.g., a tissue sample, a tumor sample, a cell, or a fluid with other biological components. As used, herein a "tumor antigen" or interchangeably, a "cancer antigen" includes any molecule present on, or associated with, a cancer, e.g., a cancer cell or a tumor microenvironment that can provoke an immune response. As used, herein an "immune cell antigen" includes any molecule present on, or associated with, an immune cell that can provoke an immune response.

The "antigen-binding site," or "binding portion" of an antibody molecule refers to the part of an antibody molecule, e.g., an immunoglobulin (Ig) molecule, that participates in antigen binding. In embodiments, the antigen binding site is formed by amino acid residues of the variable (V) regions of the heavy (H) and light (L) chains. Three highly divergent stretches within the variable regions of the heavy and light chains, referred to as hypervariable regions, are disposed between more conserved flanking stretches called "framework regions," (FRs). FRs are amino acid sequences that are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In embodiments, in an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface, which is complementary to the three-dimensional surface of a bound antigen. The three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." The framework region and CDRs have been defined and described, e.g., in Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242, and Chothia, C. et al. (1987) J. Mol. Biol. 196:901-917. Each variable chain (e.g., variable heavy chain and variable light chain) is typically made up of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the amino acid order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

"Cancer" as used herein can encompass all types of oncogenic processes and/or cancerous growths. In embodiments, cancer includes primary tumors as well as metastatic tissues or malignantly transformed cells, tissues, or organs. In embodiments, cancer encompasses all histopathologies and stages, e.g., stages of invasiveness/severity, of a cancer. In embodiments, cancer includes relapsed and/or resistant cancer. The terms "cancer" and "tumor" can be used interchangeably. For example, both terms encompass solid and liquid tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors.

As used herein, an "immune cell" refers to any of various cells that function in the immune system, e.g., to protect against agents of infection and foreign matter. In embodiments, this term includes leukocytes, e.g., neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Innate leukocytes include phagocytes (e.g., macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. Innate leukocytes identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms, and are mediators in the activation of an adaptive immune response. The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are important types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response. The term "immune cell" includes immune effector cells.

"Immune effector cell," as that term is used herein, refers to a cell that is involved in an immune response, e.g., in the promotion of an immune effector response. Examples of immune effector cells include, but are not limited to, T cells, e.g., alpha/beta T cells and gamma/delta T cells, B cells, natural killer (NK) cells, natural killer T (NK T) cells, and mast cells.

The term "effector function" or "effector response" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines.

The compositions and methods of the present invention encompass polypeptides and nucleic acids having the sequences specified, or sequences substantially identical or similar thereto, e.g., sequences at least 80%, 85%, 90%, 95% identical or higher to the sequence specified. In the context of an amino acid sequence, the term "substantially identical" is used herein to refer to a first amino acid that contains a sufficient or minimum number of amino acid residues that are i) identical to, or ii) conservative substitutions of aligned amino acid residues in a second amino acid sequence such that the first and second amino acid sequences can have a common structural domain and/or common functional activity. For example, amino acid sequences that contain a common structural domain having at least about 80%, 85%, 90%. 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, e.g., a sequence provided herein.

In the context of nucleotide sequence, the term "substantially identical" is used herein to refer to a first nucleic acid sequence that contains a sufficient or minimum number of

nucleotides that are identical to aligned nucleotides in a second nucleic acid sequence such that the first and second nucleotide sequences encode a polypeptide having common functional activity, or encode a common structural polypeptide domain or a common functional polypeptide activity. For example, nucleotide sequences having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identity to a reference sequence, e.g., a sequence provided herein.

The term "variant" refers to a polypeptide that has a substantially identical amino acid sequence to a reference amino acid sequence, or is encoded by a substantially identical nucleotide sequence. In some embodiments, the variant is a functional variant.

The term "functional variant" refers to a polypeptide that has a substantially identical amino acid sequence to a reference amino acid sequence, or is encoded by a substantially identical nucleotide sequence, and is capable of having one or more activities of the reference amino acid sequence.

Calculations of homology or sequence identity between sequences (the terms are used interchangeably herein) are performed as follows.

To determine the percent identity of two amino acid sequences, or of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more preferably at least 50%, 60%, and even more preferably at least 70%, 80%, 90%, 100% of the length of the reference sequence. The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology").

The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* 48:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. A particularly preferred set of parameters (and the one that should be used unless otherwise specified) are a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5.

The percent identity between two amino acid or nucleotide sequences can be determined using the algorithm of E. Meyers and W. Miller ((1989) *CABIOS,* 4:11-17) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences described herein can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and) (BLAST programs (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215: 403-10. BLAST nucleotide searches can be performed with the NBLAST program, score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention. BLAST protein searches can be performed with the)(BLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul et al., (1997) *Nucleic Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used.

It is understood that the molecules of the present invention may have additional conservative or non-essential amino acid substitutions, which do not have a substantial effect on their functions.

The term "amino acid" is intended to embrace all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains; and all stereoisomers of any of any of the foregoing. As used herein the term "amino acid" includes both the D- or L-optical isomers and peptidomimetics.

A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine).

The terms "polypeptide", "peptide" and "protein" (if single chain) are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation, such as conjugation with a labeling component. The polypeptide can be isolated from natural sources, can be a produced by recombinant techniques from a eukaryotic or prokaryotic host, or can be a product of synthetic procedures.

The terms "nucleic acid," "nucleic acid sequence," "nucleotide sequence," or "polynucleotide sequence," and "polynucleotide" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The

polynucleotide may be either single-stranded or double-stranded, and if single-stranded may be the coding strand or non-coding (antisense) strand. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. The nucleic acid may be a recombinant polynucleotide, or a polynucleotide of genomic, cDNA, semisynthetic, or synthetic origin which either does not occur in nature or is linked to another polynucleotide in a non-natural arrangement.

The term "isolated," as used herein, refers to material that is removed from its original or native environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated by human intervention from some or all of the co-existing materials in the natural system, is isolated. Such polynucleotides could be part of a vector and/or such polynucleotides or polypeptides could be part of a composition, and still be isolated in that such vector or composition is not part of the environment in which it is found in nature.

Various aspects of the invention are described in further detail below. Additional definitions are set out throughout the specification.

Human T Cell Receptor (TCR) Complex

T cell receptors (TCR) can be found on the surface of T cells. TCRs recognize antigens, e.g., peptides, presented on, e.g., bound to, major histocompatibility complex (MHC) molecules on the surface of cells, e.g., antigen-presenting cells. TCRs are heterodimeric molecules and can comprise an alpha chain, a beta chain, a gamma chain or a delta chain. TCRs comprising an alpha chain and a beta chain are also referred to as TCRαβ. The TCR beta chain consists of the following regions (also known as segments): variable (V), diversity (D), joining (J) and constant (C) (see Mayer G. and Nyland J. (2010) Chapter 10: Major Histocompatibility Complex and T-cell Receptors-Role in Immune Responses. In: Microbiology and Immunology on-line, University of South Carolina School of Medicine). The TCR alpha chain consists of V, J and C regions. The rearrangement of the T-cell receptor (TCR) through somatic recombination of V (variable), D (diversity), J (joining), and C (constant) regions is a defining event in the development and maturation of a T cell. TCR gene rearrangement takes place in the thymus.

TCRs can comprise a receptor complex, known as the TCR complex, which comprises a TCR heterodimer comprising of an alpha chain and a beta chain, and dimeric signaling molecules, e.g., CD3 co-receptors, e.g., CD3δ/ε, and/or CD3γ/ε.

TCR Beta V (TCRβV)

Diversity in the immune system enables protection against a huge array of pathogens. Since the germline genome is limited in size, diversity is achieved not only by the process of V(D)J recombination but also by junctional (junctions between V-D and D-J segments) deletion of nucleotides and addition of pseudo-random, non-templated nucleotides. The TCR beta gene undergoes gene arrangement to generate diversity.

The TCR V beta repertoire varies between individuals and populations because of, e.g., 7 frequently occurring inactivating polymorphisms in functional gene segments and a large insertion/deletion-related polymorphism encompassing 2 V beta gene segments.

This disclosure provides, inter alia, antibody molecules and fragments thereof, that bind, e.g., specifically bind, to a human TCR beta V chain (TCRβV), e.g., a TCRβV gene family (also referred to as a group), e.g., a TCRβV subfamily (also referred to as a subgroup), e.g., as described herein. TCR beta V families and subfamilies are known in the art, e.g., as described in Yassai et al., (2009) *Immunogenetics* 61(7) pp: 493-502; Wei S. and Concannon P. (1994) *Human Immunology* 41(3) pp: 201-206. The antibodies described herein can be recombinant antibodies, e.g., recombinant non-murine antibodies, e.g., recombinant human or humanized antibodies.

In an aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to human TCRβV, e.g., a TCRβV family, e.g., gene family or a variant thereof. In some embodiments a TCRBV gene family comprises one or more subfamilies, e.g., as described herein, e.g., in FIG. **3**, Table 8A or Table 8B. In some embodiments, the TCRβV gene family comprises: a TCRβV6 subfamily, a TCRβV10 subfamily, a TCRβV12 subfamily, a TCRβV5 subfamily, a TCRβV7 subfamily, a TCRβV11 subfamily, a TCRβV14 subfamily, a TCRβV16 subfamily, a TCRβV18 subfamily, a TCRβV9 subfamily, a TCRβV13 subfamily, a TCRβV4 subfamily, a TCRβV3 subfamily, a TCRβV2 subfamily, a TCRβV15 subfamily, a TCRβV30 subfamily, a TCRβV19 subfamily, a TCRβV27 subfamily, a TCRβV28 subfamily, a TCRβV24 subfamily, a TCRβV20 subfamily, TCRβV25 subfamily, a TCRβV29 subfamily, a TCRβV1 subfamily, a TCRβV17 subfamily, a TCRβV21 subfamily, a TCRβV23 subfamily, or a TCRβV26 subfamily.

In some embodiments, TCRβV6 subfamily is also known as TCRβV13.1. In some embodiments, the TCRβV6 subfamily comprises: TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβ V6-8*01, TCRβ V6-5*01, TCRβ V6-6*02, TCRβ V6-6*01, TCRβ V6-2*01, TCRβV6-3*01 or TCRβV6-1*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-9*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-8*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-5*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-2*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-3*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-1*01, or a variant thereof.

In some embodiments, TCRβV6 comprises TCRβV6-5*01, or a variant thereof. In some embodiments, TCRβV6, e.g., TCRβV6-5*01, is recognized, e.g., bound, by SEQ ID NO: 1 and/or SEQ ID NO: 2. In some embodiments, TCRβV6, e.g., TCRβV6-5*01, is recognized, e.g., bound, by SEQ ID NO: 9 and/or SEQ ID NO: 10. In some embodiments, TCRβV6 is recognized, e.g., bound, by SEQ ID NO: 9 and/or SEQ ID NO: 11.

In some embodiments, TCRβV10 subfamily is also known as TCRβV12. In some embodiments, the TCRβV10 subfamily comprises: TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01, or a variant thereof.

In some embodiments, TCRβV12 subfamily is also known as TCRβV8.1. In some embodiments, the TCRβV12 subfamily comprises: TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01, or a variant thereof. In some embodiments, TCRβV12 is recognized, e.g., bound, by SEQ ID NO: 15

and/or SEQ ID NO: 16. In some embodiments, TCRβV12 is recognized, e.g., bound, by any one of SEQ ID NOs 23-25, and/or any one of SEQ ID NO: 26-30:

In some embodiments, the TCRβV5 subfamily is chosen from: TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01, or a variant thereof.

In some embodiments, the TCRβV7 subfamily comprises TCRβV7-7*01, TCRβV7-6*01, TCRβV7-8*02, TCRβV7-4*01, TCRβV7-2*02, TCRβV7-2*03, TCRβV7-2*01, TCRβV7-3*01, TCRβV7-9*03, or TCRβV7-9*01, or a variant thereof.

In some embodiments, the TCRβV11 subfamily comprises: TCRβV11-1*01, TCRβV11-2*01 or TCRβV11-3*01, or a variant thereof.

In some embodiments, the TCRβV14 subfamily comprises TCRβV14*01, or a variant thereof.

In some embodiments, the TCRβV16 subfamily comprises TCRβV16*01, or a variant thereof.

In some embodiments, the TCRβV18 subfamily comprises TCRβV18*01, or a variant thereof.

In some embodiments, the TCRβV9 subfamily comprises TCRβV9*01 or TCRβV9*02, or a variant thereof.

In some embodiments, the TCRβV13 subfamily comprises TCRβV13*01, or a variant thereof.

In some embodiments, the TCRβV4 subfamily comprises TCRβV4-2*01, TCRβV4-3*01, or TCRβV4-1*01, or a variant thereof.

In some embodiments, the TCRβV3 subfamily comprises TCRβV3-1*01, or a variant thereof.

In some embodiments, the TCRβV2 subfamily comprises TCRβV2*01, or a variant thereof.

In some embodiments, the TCRβV15 subfamily comprises TCRβV15*01, or a variant thereof.

In some embodiments, the TCRβV30 subfamily comprises TCRβV30*01, or TCRβV30*02, or a variant thereof.

In some embodiments, the TCRβV19 subfamily comprises TCRβV19*01, or TCRβV19*02, or a variant thereof.

In some embodiments, the TCRβV27 subfamily comprises TCRβV27*01, or a variant thereof.

In some embodiments, the TCRβV28 subfamily comprises TCRβV28*01, or a variant thereof.

In some embodiments, the TCRβV24 subfamily comprises TCRβV24-1*01, or a variant thereof.

In some embodiments, the TCRβV20 subfamily comprises TCRβV20-1*01, or TCRβV20-1*02, or a variant thereof.

In some embodiments, the TCRβV25 subfamily comprises TCRβV25-1*01, or a variant thereof.

In some embodiments, the TCRβV29 subfamily comprises TCRβV29-1*01, or a variant thereof.

TABLE 8A

List of TCRβV subfamilies and subfamily members

Reference in FIG. 3	Subfamily	Subfamily members
A	TCRβ V6 Also referred to as: TCR VB 13.1	TCRβ V6-4*01, TCRβ V6-4*02, TCRβ V6-9*01, TCRβ V6-8*01, TCRβ V6-5*01, TCRβ V6-6*02, TCRβ V6-6*01, TCRβ V6-2*01, TCRβ V6-3*01 or TCRβ V6-1*01.
B	TCRβ V10 Also referred to as: TCRβ V12	TCRβ V10-1*01, TCRβ V10-1*02, TCRβ V10-3*01 or TCRβ V10-2*01
C	TCRβ V12 Also referred to as: TCRβ V8.1	TCRβ V12-4*01, TCRβ V12-3*01, or TCRβ V12-5*01

TABLE 8A-continued

List of TCRβV subfamilies and subfamily members

Reference in FIG. 3	Subfamily	Subfamily members
D	TCRβ V5	TCRβ V5-5*01, TCRβ V5-6*01, TCRβ V5-4*01, TCRβ V5-8*01, TCRβ V5-1*01
E	TCRβ V7	TCRβ V7-7*01, TCRβ V7-6*01, TCRβ V7 -8*02, TCRβ V7 -4*01, TCRβ V7-2*02, TCRβ V7-2*03, TCRβ V7-2*01, TCRβ V7-3*01, TCRβ V7-9*03, or TCRβ V7-9*01
F	TCRβ V11	TCRβ V11-1*01, TCRβ V11-2*01 or TCRβ V11-3*01
G	TCRβ V14	TCRβ V14*01
H	TCRβ V16	TCRβ V16*01
I	TCRβ V18	TCRβ V18*01
J	TCRβ V9	TCRβ V9*01 or TCRβ V9*02
K	TCRβ V13	TCRβ V13*01
L	TCRβ V4	TCRβ V4-2*01, TCRβ V4-3*01, or TCRβ V4-1*01
M	TCRβ V3	TCRβ V3-1*01
N	TCRβ V2	TCRβ V2*01
O	TCRβ V15	TCRβ V15*01
P	TCRβ V30	TCRβ V30*01, or TCRβ V30*02
Q	TCRβ V19	TCRβ V19*01, or TCRβ V19*02
R	TCRβ V27	TCRβ V27*01.
S	TCRβ V28	TCRβ V28*01.
T	TCRβ V24	TCRβ V24-1*01
U	TCRβ V20	TCRβ V20-1*01, or TCRβ V20-1*02
V	TCRβ V25	TCRβ V25-1*01
W	TCRβ V29	TCRβ V29-1*01

TABLE 8B

Additional TCRβV subfamilies Subfamily
TCRβ V1
TCRβ V17
TCRβ V21
TCRβ V23
TCRβ V26

Exemplary amino acid sequences for TCRβV subfamily members can be found on the ImMunoGeneTics Information System website: www.imgt.org/, or in a similar resource.

The alignment of TCRBV amino acid sequences in Table 9 underscores the diversity of TCR sequences. In particular, the TRBV sequences from different subfamilies are considerably different from each other.

Anti-TCRβV Antibodies

Disclosed herein, is the discovery of a novel class of antibodies, i.e. anti-TCRβV antibody molecules disclosed herein, which despite having low sequence similarity (e.g., low sequence identity among the different antibody molecules that recognize different TCRβV subfamilies), recognize a structurally conserved region, e.g., domain, on the TCRβV protein (e.g., as denoted by the circled area in FIG. **24**A) and have a similar function (e.g., a similar cytokine profile). Thus, the anti-TCRβV antibody molecules disclosed herein share a structure-function relationship.

Without wishing to be bound by theory, it is believed that in some embodiments, the anti-TCRβV antibody molecules disclosed herein bind to an outward facing epitope of a TCRβV protein when it is in a complex with a TCRalpha protein, e.g., as described by the circled area in FIG. **24**A. In some embodiments, the anti-TCRβV antibody molecules disclosed herein recognize (e.g., bind to), a structurally

conserved domain on the TCRβV protein (e.g., as denoted by the circled area in FIG. **24**A).

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, an interface of a TCRβV:TCRalpha complex.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, a constant region of a TCRβV protein. An exemplary antibody that binds to a constant region of a TCRBV region is JOVI. 1 as described in Viney et al., (*Hybridoma.* 1992 December; 11(6):701-13).

In some embodiments, the anti-TCRβV antibody molecules disclosed herein do not recognize, e.g., bind to, one or more (e.g., all) of a complementarity determining region (e.g., CDR1, CDR2 and/or CDR3) of a TCRβV protein.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein binds (e.g., specifically binds) to a TCRβV region. In some embodiments, binding of anti-TCRβV antibody molecules disclosed herein results in a cytokine profile that differs from a cytokine profile of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager"). In some embodiments, the non-TCRβV-binding T cell engager comprises an antibody that binds to a CD3 molecule (e.g., CD3 epsilon (CD3e) molecule); or a TCR alpha (TCRα) molecule. In some embodiments, the non-TCRβV-binding T cell engager is an OKT3 antibody or an SP34-2 antibody.

In an aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to human TCRβV, e.g., a TCRβV gene family, e.g., one or more of a TCRβV subfamily, e.g., as described herein, e.g., in FIG. **3**, Table 8A, or Table 8B. In some embodiments, the anti-TCRβV antibody molecule binds to one or more TCRβV subfamilies chosen from: a TCRβV6 subfamily, a TCRβV10 subfamily, a TCRβV12 subfamily, a TCRβV5 subfamily, a TCRβV7 subfamily, a TCRβV11 subfamily, a TCRβV14 subfamily, a TCRβV16 subfamily, a TCRβV18 subfamily, a TCRβV9 subfamily, a TCRβV13 subfamily, a TCRβV4 subfamily, a TCRβV3 subfamily, a TCRβV2 subfamily, a TCRβV15 subfamily, a TCRβV30 subfamily, a TCRβV19 subfamily, a TCRβV27 subfamily, a TCRβV28 subfamily, a TCRβV24 subfamily, a TCRβV20 subfamily, TCRβV25 subfamily, a TCRβV29 subfamily, a TCRβV1 subfamily, a TCRβV17 subfamily, a TCRβV21 subfamily, a TCRβV23 subfamily, or a TCRβV26 subfamily, or a variant thereof.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV6 subfamily comprising: TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01, or a variant thereof. In some embodiments the TCRβV6 subfamily comprises TCRβV6-5*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-9*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-8*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-5*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-2*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-3*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-1*01, or a variant thereof.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV10 subfamily comprising: TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01, or a variant thereof.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV12 subfamily comprising: TCRβV12-4*01, TCRβV12-3*01 or TCRβV12-5*01, or a variant thereof.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV5 subfamily comprising: TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01, or a variant thereof.

Exemplary anti-TCRβV antibody molecules and the corresponding TCRβV subfamily recognized by said anti-TCRβV antibody molecules is disclosed in Table 13.

TABLE 13

Exemplary anti-TCRβV antibody molecules				
TRBV gene name	TRBV allele name	Reagents monoclonal antibodies: Clone name and Specificity	Company product	Isotype
TRBV2	TRBV2*01	IsMMU 546 (TRBV2)	Serotec V BETA 22	Mouse
	TRBV2*02		Coulter Vbeta22	IgG1
	TRBV2*03			
TRBV3-1	TRBV3-1*01	FIN9 (TRBV3-1)	Serotec Vbeta9	Mouse
		AMKB1-2 (TRBV3-1)	Coulter Vbeta9	IgG2a
	TRBV3-1*02		BD Biosciences	Mouse
			Vbeta9	IgG1
TRBV4-1	TRBV4-1*01	ZOE (TRBV4-1, TRBV4-2,	Serotec V BETA 7	Mouse
		TRBV4-3)	Coulter Vbeta7	IgG2a
	TRBV4-1*02	3G5 (TRBV4-1)	Pierce EndogenV beta	Mouse
			7.1	IgG2b
TRBV4-2	TRBV4-2*01	ZOE (TRBV4-1, TRBV4-2,	Serotec V BETA 7	Mouse
	TRBV4-2*02	TRBV4-3)	Coulter Vbeta7	IgG2a
TRBV4-3	TRBV4-3*01	ZOE (TRBV4-1, TRBV4-2,	Serotec V BETA 7	Mouse
	TRBV4-3*02	TRBV4-3)	Coulter Vbeta7	IgG2a
	TRBV4-3*03			
	TRBV4-3*04	ZIZOU4 (TRBV4-3)	Coulter Vbeta7.2	Mouse
				IgG2a

TABLE 13-continued

Exemplary anti-TCRβV antibody molecules				
TRBV gene name	TRBV allele name	Reagents monoclonal antibodies: Clone name and Specificity	Company product	Isotype
TRBV5-1	TRBV5-1*01	IMMU157 (TRBV5-1)	Serotec Vbeta5.1 Coulter Vbeta5.1	Mouse IgG2a
	TRBV5-1*02	LC4 (TRBV5-1)	Pierce Endogen V beta 5(c) BD Biosciences Vbeta5(c)	Mouse IgG1
TRBV5-4	TRBV5-4*01 TRBV5-4*02 TRBV5-4*03 TRBV5-4*04			
TRBV5-5	TRBV5-5*01	3D11 (TRBV5-5) 1C1 (TRBV5-5, TRBV5-6)	Serotec VBETA5.3 Coulter Vbeta5.3	Mouse IgG1
	TRBV5-5*02	W112 (TRBV5-5) MH3-2 (TRBV5-5, TRBV5-6) 4H11 (TM27) as disclosed in	Pierce Endogen V beta 5(a) BD Biosciences Vbeta5(a)	Mouse IgG1
	TRBV5-5*03	U.S. Pat. No. 5,861,155	Pierce Endogen V beta 5(b) Serotec V beta 5.2/5.3 BD Biosciences Vbeta5(b) BD Biosciences Vbeta5	Mouse IgG1 Mouse IgG2a
TRBV5-6	TRBV5-6*01	36213 (TRBV5-6) 1C1 (TRBV5-5, TRBV5-6) MH3-2 (TRBV5-5, TRBV5-6)	Serotec Vbeta5.2 BD Biosciences Vbeta5(a) BD Biosciences Vbeta5	Mouse IgG1 Mouse IgG1 Mouse IgG2a
TRBV5-8	TRBV5-8*01 TRBV5-8*02			
TRBV6-1	TRBV6-1*01	BAM13 (TRBV6-1, TRBV6-5)	Pierce Endogen V beta 13 BD Biosciences Vbeta13.1, 13.3	Mouse IgG1
TRBV6-2	TRBV6-2*01	H132	Coulter Vbeta13.2	Mouse IgG1
TRBV6-3	TRBV6-3*01			
TRBV6-4	TRBV6-4*01 TRBV6-4*02			
TRBV6-5	TRBV6-5*01	IMMU 222 (TRBV6-5, TRBV6-6 and TRBV6-9) BAM13 (TRBV6-1, TRBV6-5)	Serotec V BETA 13.1 Coulter Vbeta13.1 Pierce Endogen V beta 13 BD Biosciences Vbeta13.1, 13.3	Mouse IgG2b Mouse IgG1
TRBV6-6	TRBV6-6*01 TRBV6-6*02 TRBV6-6*03 TRBV6-6*04 TRBV6-6*05	JU-74 (TRBV6-6) JU74.3 (TRBV6-6) IMMU 222 (TRBV6-5, TRBV6-6 and TRBV6-9)	Serotec Vbeta13.6 Coulter Vbeta13.6 Serotec V BETA 13.1 Coulter Vbeta13.1	Mouse IgG1 Mouse IgG2b
TRBV6-8	TRBV6-8*01			
TRBV6-9	TRBV6-9*01	IMMU 222 (TRBV6-5, TRBV6-6 and TRBV6-9)	Serotec V BETA 13.1 Coulter Vbeta13.1	Mouse IgG2b
TRBV7-2	TRBV7-2*01 TRBV7-2*02 TRBV7-2*03 TRBV7-2*04	OT145 (TRBV7-2)	Pierce Endogen V beta 6.7 BD Biosciences Vbeta6.7	Mouse IgG1
TRBV7-3	TRBV7-3*01 TRBV7-3*04 TRBV7-3*05			
TRBV7-4	TRBV7-4*01			
TRBV7-6	TRBV7-6*01 TRBV7-6*02			
TRBV7-7	TRBV7-7*01 TRBV7-7*02			
TRBV7-8	TRBV7-8*01 TRBV7-8*02 TRBV7-8*03			
TRBV7-9	TRBV7-9*01 TRBV7-9*02 TRBV7-9*03 TRVB7-9*04 TRBV7-9*05			

TABLE 13-continued

Exemplary anti-TCRβV antibody molecules				
TRBV	TRBV	Reagents monoclonal antibodies		
gene name	allele name	Clone name and Specificity	Company product	Isotype
	TRBV7-9*06			
	TRBV7-9*07			
TRBV9	TRBV9*01	BL37.2 (TRBV9)	Serotec Vbeta1	Rat IgG1
	TRBV9*02		Coulter Vbeta1	
	TRBV9*03			
TRBV10-1	TRBV10-1*01	S511 (TRBV10-1,	Pierce Endogen V beta 12	Mouse
	TRBV10-1*02	TRBV10-2, TRBV10-3)	BD Biosciences	IgG2b
TRBV10-2	TRBV10-2*01		Vbeta12	
	TRBV10-2*02			
TRBV10-3	TRBV10-3*01	VER2.32.1 (TRBV10-3)	Serotec Vbeta12	Mouse
	TRBV10-3*02	S511 (TRBV10-1,	Coulter Vbeta12	IgG2a
	TRBV10-3*03	TRBV10-2, TRBV10-3)	Pierce Endogen V beta 12	Mouse
	TRBV10-3*04		BD Biosciences	IgG2b
			Vbeta12	
TRBV11-1	TRBV11-1*01			
TRBV11-2	TRBV11-2*01	IG125 (TRBV11-2)	Serotec Vbeta21.3	Mouse
	TRBV11-2*02		Coulter Vbeta21.3	IgG2a
	TRBV11-2*03			
TRBV11-3	TRBV11-3*01			
	TRBV11-3*02			
	TRBV11-3*03			
	TRBV11-3*04			
TRBV12-3	TRBV12-3*01	56C5 (TRBV12-3,	Serotec Vbeta8.1/8.2	Mouse
		TRBV12-4)	Coulter Vbeta8	IgG2a
TRBV12-4	TRBV12-4*01	56C5.2 (TRBV12-3,	Pierce Endogen V beta	Mouse
		TRBV12-4)	8(a)	IgG2b
		16G8 (TRBV12-3,	BD Biosciences	
		TRBV12-4)	Vbeta8	
	TRBV12-4*02	MX-6 (TRBV12-3,	Pierce Endogen V beta	Mouse
		TRBV12-4)	8(b)	IgG2a
		JR2 (TRBV12-3, TRBV12-	BD Biosciences	Mouse
		4, TRBV12-5)	Vbeta8	IgG2b
TRBV12-5	TRBV12-5*01	JR2 (TRBV12-3, TRBV12-	BD Biosciences	Mouse
		4, TRBV12-5)	Vbeta8	IgG2b
TRBV13	TRBV13*01	AF-23 (TRBV13)	Serotec Vbeta23	Mouse
	TRBV13*02	AF23 (TRBV13)	Coulter Vbeta23	IgG1
		AHUT7 (Vbeta23)	BD Biosciences	
			Vbeta23	
TRBV14	TRBV14*01	TAMAYA1.2 (TRBV14)	Serotec Vbeta16	Mouse
	TRBV14*02		Coulter Vbeta16	IgG1
TRBV15	TRBV15*01			
	TRBV15*02			
	TRBV15*03			
TRBV16	TRBV16*01			
	TRBV16*03			
TRBV18	TRBV18*01	BA62 (TRBV18)	Serotec V BETA 18	Mouse
		BA62.6 (TRBV18)	Coulter Vbeta18	IgG1
TRBV19	TRBV19*01	C1 (TRBV19)	Pierce Endogen V beta	Mouse
			17	IgG1
			BD Biosciences	
			Vbeta17	
	TRBV19*02	E17.5F3 (TRBV19)	Serotec Vbeta17	Mouse
	TRBV19*03	E17.5F3.15.13 (TRBV19)	Coulter Vbeta17	IgG1
TRBV20-1	TRBV20-1*01	MPB2D5 (TRBV20-1)	Serotec VBETA2	Mouse
	TRBV20-1*02		Coulter Vbeta2	IgG1
	TRBV20-1*03			
	TRBV20-1*04			
	TRBV20-1*05			
	TRBV20-1*06			
	TRBV20-1*07			
TRBV24-1	TRBV24-1*01			
TRBV25-1	TRBV25-1*01	C21 (TRBV25-1)	Serotec V BETA 11	Mouse
			Coulter Vbeta11	IgG2a
TRBV27	TRBV27*01	CAS1.1.3 (TRBV27)	Serotec Vbeta14	Mouse
			Coulter Vbeta14	IgG1
TRBV28	TRBV28*01	CH92 (TRBV28)	Serotec Vbeta3	Mouse
		8F10 (TRBV28)	Coulter Vbeta3	IgM
		JOVI-3 (TRBV28)	Pierce Endogen V beta	Mouse
			3.1	IgG1
			BD Biosciences	Mouse
			Vbeta3	IgG2a
TRBV29-1	TRBV29-1*01	WJF24	Coulter Vbeta4	Rat IgM
	TRBV29-1*02			
	TRBV29-1*03			

TABLE 13-continued

Exemplary anti-TCRβV antibody molecules				
TRBV	TRBV	Reagents monoclonal antibodies		
gene name	allele name	Clone name and Specificity	Company product	Isotype
TRBV30	TRBV30*01 TRBV30*02 TRBV30*04 TRBV30*05	ELL1.4 (TRBV30)	Serotec Vbeta20 Coulter Vbeta20	Mouse IgG1

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV12, or binds to TCRβV12 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV12 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV12 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01, or binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV5-5*01 or TCRβV5-1*01 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

Anti-TCRβV6 Antibodies

Accordingly, in one aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to human TCRβV6, e.g., a TCRβV6 subfamily comprising: TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments the TCRβV6 subfamily comprises TCRβV6-5*01 or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-4*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-9*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-8*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-5*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*02, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-6*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-2*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-3*01, or a variant thereof. In some embodiments, TCRβV6 comprises TCRβV6-1*01, or a variant thereof.

In some embodiments, TCRβV6-5*01 is encoded by the nucleic acid sequence of SEQ ID NO: 43, or a sequence having 85%, 90%, 95%, 99% or more identity thereof.

SEQ ID NO: 43

```
ATGAGCATCGGCCTCCTGTGCTGTGCAGCCTTGTCTCTCCTGTGGGCAGG

TCCAGTGAATGCTGGTGTCACTCAGACCCCAAAATTCCAGGTCCTGAAGA

CAGGACAGAGCATGACACTGCAGTGTGCCCAGGATATGAACCATGAATAC

ATGTCCTGGTATCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCATTA

CTCAGTTGGTGCTGGTATCACTGACCAAGGAGAAGTCCCCAATGGCTACA

ATGTCTCCAGATCAACCACAGAGGATTTCCCGCTCAGGCTGCTGTCGGCT

GCTCCCTCCCAGACATCTGTGTACTTCTGTGCCAGCAGTTACTC
```

In some embodiments, TCRβV6-5*01 comprises the amino acid sequence of SEQ ID NO: 44, or an amino acid sequence having 85%, 90%, 95%, 99% or more identity thereof.

SEQ ID NO: 44

```
MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQDMNHEY

MSWYRQDPGMGLRLIHYSVGAGITDQGEVPNGYNVSRSTTEDFPLRLLSA

APSQTSVYFCASSY
```

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, is a non-murine antibody molecule, e.g., a human or humanized antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule is a human antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule is a humanized antibody molecule.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, is isolated or recombinant.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises at least one antigen-binding region, e.g., a variable region or an antigen-binding fragment thereof, from an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises at least one, two, three or four variable regions from an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises at least one or two heavy chain variable regions from an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody molecule described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule comprises a heavy chain variable region (VH) having a consensus sequence of SEQ ID NO: 231 or 3290.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises at least one or two light chain variable regions from an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule comprises a light chain variable region (VL) having a consensus sequence of SEQ ID NO: 230 or 3289.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a heavy chain constant region for an IgG4, e.g., a human IgG4. In still another embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes a heavy chain constant region for an IgG1, e.g., a human IgG1. In one embodiment, the heavy chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes a kappa light chain constant region, e.g., a human kappa light chain constant region. In one embodiment, the light chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region (VH) of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, or three CDRs (or collectively all of the CDRs) from a heavy chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, or three complementarity determining regions (CDRs) from a light chain variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 1, or encoded by a nucleotide sequence shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, molecule includes all six CDRs from an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1, or closely related CDRs, e.g., CDRs which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions). In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes at least one, two, or three CDRs according to Kabat et al. (e.g., at least one, two, or three CDRs according to the Kabat definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes at least one, two, or three CDRs according to Kabat et al. (e.g., at least one, two, or three CDRs according to the Kabat definition as set out in Table 1) from a light chain variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, three, four, five, or six CDRs according to Kabat et al. (e.g., at least one, two, three, four, five, or six CDRs according to the Kabat definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Kabat et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes all six CDRs according to Kabat et al. (e.g., all six CDRs according to the Kabat definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to Kabat et al. shown in Table 1. In one embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding hypervariable loop of an antibody described herein, e.g., an antibody chosen from chosen from A-H.1 or A-H.2 e.g., the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. See, e.g., Chothia et al., (1992) J. Mol. Biol. 227:799-817; Tomlinson et al., (1992) J. Mol. Biol. 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes at least one, two, or three CDRs according to Chothia et al. (e.g., at least one, two, or three CDRs according to the Chothia definition as set out in Table 1) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or as described in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Chothia et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes at least one, two, or three CDRs according to Chothia et al. (e.g., at least one, two, or three CDRs according to the Chothia definition as set out in Table 1) from a light chain variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Chothia et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes at least one, two, three, four, five, or six CDRs according to Chothia et al. (e.g., at least one, two, three, four, five, or six CDRs according to the Chothia definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by the nucleotide sequence in Table 1; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Chothia et al. shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes all six CDRs according to Chothia et al. (e.g., all six CDRs according to the Chothia definition as set out in Table 1) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or an antibody described in Table 1, or encoded by a nucleotide sequence in Table 1; or

a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to Chothia et al. shown in Table 1. In one embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, molecule includes a combination of CDRs or hypervariable loops defined according to Kabat et al., Chothia et al., or as described in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, can contain any combination of CDRs or hypervariable loops according to the Kabat and Chothia definitions.

In some embodiments, a combined CDR as set out in Table 1 is a CDR that comprises a Kabat CDR and a Chothia CDR.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, molecule includes a combination of CDRs or hypervariable loops identified as combined CDRs in Table 1. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, can contain any combination of CDRs or hypervariable loops according the "combined" CDRs are described in Table 1.

In an embodiment, e.g., an embodiment comprising a variable region, a CDR (e.g., a combined CDR, Chothia CDR or Kabat CDR), or other sequence referred to herein, e.g., in Table 1, the antibody molecule is a monospecific antibody molecule, a bispecific antibody molecule, a bivalent antibody molecule, a biparatopic antibody molecule, or an antibody molecule that comprises an antigen binding fragment of an antibody, e.g., a half antibody or antigen binding fragment of a half antibody. In certain embodiments the antibody molecule comprises a multispecific molecule, e.g., a bispecific molecule, e.g., as described herein.

In an embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes:

(i) one, two or all of a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11, and/or

(ii) one, two or all of a heavy chain complementarity determining region 1 (HC CDR1), heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1 or SEQ ID NO: 9.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises a LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NO: 2, and a HC CDR1, HC CDR2, and HC CDR3 of SEQ ID NO: 1.

In some embodiments the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises a LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NO: 10, and a HC CDR1, HC CDR2, and HC CDR3 of SEQ ID NO: 9.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises a LC CDR1, LC CDR2, and LC CDR3 of SEQ ID NO: 11, and a HC CDR1, HC CDR2, and HC CDR3 of SEQ ID NO: 9.

In an embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 6, a LC CDR2 amino acid sequence of SEQ ID NO: 7, or a LC CDR3 amino acid sequence of SEQ ID NO: 8; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 3, a HC CDR2 amino acid sequence of SEQ ID NO: 4, or a HC CDR3 amino acid sequence of SEQ ID NO: 5.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 6, a LC CDR2 amino acid sequence of SEQ ID NO: 7, or a LC CDR3 amino acid sequence of SEQ ID NO: 8; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 3, a HC CDR2 amino acid sequence of SEQ ID NO: 4, or a HC CDR3 amino acid sequence of SEQ ID NO: 5.

In an embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 51, a LC CDR2 amino acid sequence of SEQ ID NO: 52, or a LC CDR3 amino acid sequence of SEQ ID NO: 53; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 45, a HC CDR2 amino acid sequence of SEQ ID NO: 46, or a HC CDR3 amino acid sequence of SEQ ID NO: 47.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 51, a LC CDR2 amino acid sequence of SEQ ID NO: 52, or a LC CDR3 amino acid sequence of SEQ ID NO: 53; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 45, a HC CDR2 amino acid sequence of SEQ ID NO: 46, or a HC CDR3 amino acid sequence of SEQ ID NO: 47.

In an embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 54, a LC CDR2 amino acid sequence of SEQ ID NO: 55, or a LC CDR3 amino acid sequence of SEQ ID NO: 56; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 48, a HC CDR2 amino acid sequence of SEQ ID NO: 49, or a HC CDR3 amino acid sequence of SEQ ID NO: 50.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 54, a LC CDR2 amino acid sequence of SEQ ID NO: 55, or a LC CDR3 amino acid sequence of SEQ ID NO: 56; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 48, a HC

CDR2 amino acid sequence of SEQ ID NO: 49, or a HC CDR3 amino acid sequence of SEQ ID NO: 50.

In one embodiment, the light or the heavy chain variable framework (e.g., the region encompassing at least FR1, FR2, FR3, and optionally FR4) of the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule can be chosen from: (a) a light or heavy chain variable framework including at least 80%, 85%, 87% 90%, 92%, 93%, 95%, 97%, 98%, or 100% of the amino acid residues from a human light or heavy chain variable framework, e.g., a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (b) a light or heavy chain variable framework including from 20% to 80%, 40% to 60%, 60% to 90%, or 70% to 95% of the amino acid residues from a human light or heavy chain variable framework, e.g., a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (c) a non-human framework (e.g., a rodent framework); or (d) a non-human framework that has been modified, e.g., to remove antigenic or cytotoxic determinants, e.g., deimmunized, or partially humanized. In one embodiment, the light or heavy chain variable framework region (particularly FR1, FR2 and/or FR3) includes a light or heavy chain variable framework sequence at least 70, 75, 80, 85, 87, 88, 90, 92, 94, 95, 96, 97, 98, 99% identical or identical to the frameworks of a VL or VH segment of a human germline gene.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a heavy chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more changes, e.g., amino acid substitutions or deletions, from an amino acid sequence of A-H.1 or A-H.2, e.g., the amino acid sequence of the FR region in the entire variable region, e.g., shown in FIG. **1**A, or in SEQ ID NO: 9.

Alternatively, or in combination with the heavy chain substitutions described herein, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more amino acid changes, e.g., amino acid substitutions or deletions, from an amino acid sequence of A-H.1 or A-H.2.e.g., the amino acid sequence of the FR region in the entire variable region, e.g., shown in FIG. **1**B, or in SEQ ID NO: 10 or SEQ ID NO: 11.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes one, two, three, or four heavy chain framework regions shown in FIG. **1**A, or a sequence substantially identical thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes one, two, three, or four light chain framework regions shown in FIG. **1**B, or a sequence substantially identical thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework region 1 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework region 2 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework region 3 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework region 4 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising a framework region, e.g., framework region 1 (FR1), comprising a change, e.g., a substitution (e.g., a conservative substitution) at position 10 according to Kabat numbering. In some embodiments, the FR1 comprises a Phenylalanine at position 10, e.g., a Serine to Phenyalanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising a framework region, e.g., framework region 2 (FR2), comprising a change, e.g., a substitution (e.g., a conservative substitution) at a position disclosed herein according to Kabat numbering. In some embodiments, FR2 comprises a Histidine at position 36, e.g., a substitution at position 36 according to Kabat numbering, e.g., a Tyrosine to Histidine substitution. In some embodiments, FR2 comprises an Alanine at position 46, e.g., a substitution at position 46 according to Kabat numbering, e.g., an Arginine to Alanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising a framework region, e.g., framework region 3 (FR3), comprising a change, e.g., a substitution (e.g., a conservative substitution) at a position disclosed herein according to Kabat numbering. In some embodiments, FR3 comprises a Phenyalanine at position 87, e.g., a substitution at position 87 according to Kabat numbering, e.g., a Tyrosine to Phenyalanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising: (a) a framework region 1 (FR1) comprising a Phenylalanine at position 10, e.g., a substitution at position 10 according to Kabat numbering, e.g., a Serine to Phenyalanine substitution; (b) a framework region 2 (FR2) comprising a Histidine at position 36, e.g., a substitution at position 36 according to Kabat numbering, e.g., a Tyrosine to Histidine substitution, and a Alanine at position 46, e.g., a substitution at position 46 according to Kabat numbering, e.g., a Arginine to Alanine substitution; and (c) a framework region 3 (FR3) comprising a Phenylalanine at position 87, e.g., a substitution at position 87 according to Kabat numbering, e.g., a Tyrosine to Phenyalanine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 10. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising: (a) a framework region 2 (FR2) comprising a Histidine at position 36, e.g., a substitution at position 36

according to Kabat numbering, e.g., a Tyrosine to Histidine substitution, and a Alanine at position 46, e.g., a substitution at position 46 according to Kabat numbering, e.g., a Arginine to Alanine substitution; and (b) a framework region 3 (FR3) comprising a Phenylalanine at position 87, e.g., a substitution at position 87 according to Kabat numbering, e.g., a Tyrosine to Phenyalanine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 11. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a light chain variable domain comprising: (a) a framework region 1 (FR1) comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more (e.g., all) positions disclosed herein according to Kabat numbering; (b) a framework region 2 (FR2) comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more (e.g., all) position disclosed herein according to Kabat numbering and (c) a framework region 3 (FR3) comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more (e.g., all) position disclosed herein according to Kabat numbering. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework region 1 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework region 2 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**A

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework region 3 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework region 4 of A-H.1 or A-H.2, e.g., as shown in FIG. **1**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a heavy chain variable domain comprising a framework region, e.g., framework region 3 (FR3), comprising a change, e.g., a substitution (e.g., a conservative substitution) at a position disclosed herein according to Kabat numbering. In some embodiments, FR3 comprises a Threonine at position 73, e.g., a substitution at position 73 according to Kabat numbering, e.g., a Glutamic Acid to Threonine substitution. In some embodiments, FR3 comprises a Glycine at position 94, e.g., a substitution at position 94 according to Kabat numbering, e.g., an Arginine to Glycine substitution. In some embodiments, the substitution is relative to a human germline heavy chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises a heavy chain variable domain comprising a framework region 3 (FR3) comprising a Threonine at position 73, e.g., a substitution at position 73 according to Kabat numbering, e.g., a Glutamic Acid to Threonine substitution, and a Glycine at position 94, e.g., a substitution at position 94 according to Kabat numbering, e.g., a Arginine to Glycine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 10.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework regions 1-4 of A-H.1 or A-H.2, e.g., SEQ ID NO: 9, or as shown in FIGS. **1**A and **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework regions 1-4 of A-H.1, e.g., SEQ ID NO: 10, or as shown in FIGS. **1**A and **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the light chain framework regions 1-4 of A-H.2, e.g., SEQ ID NO: 11, or as shown in FIGS. **1**A and **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework regions 1-4 of A-H.1, e.g., SEQ ID NO: 9; and the light chain framework regions 1-4 of A-H.1, e.g., SEQ ID NO: 10, or as shown in FIGS. **1**A and **1**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises the heavy chain framework regions 1-4 of A-H.2, e.g., SEQ ID NO: 9; and the light chain framework regions 1-4 of A-H.2, e.g., SEQ ID NO: 11, or as shown in FIGS. **1**A and **1**B.

In some embodiments, the heavy or light chain variable domain, or both, of the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, includes an amino acid sequence, which is substantially identical to an amino acid disclosed herein, e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a variable region of an antibody described herein, e.g., an antibody chosen from A-H.1 or A-H.2, or as described in Table 1, or encoded by the nucleotide sequence in Table 1; or which differs at least 1 or 5 residues, but less than 40, 30, 20, or 10 residues, from a variable region of an antibody described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises at least one, two, three, or four antigen-binding regions, e.g., variable regions, having an amino acid sequence as set forth in Table 1, or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the sequences shown in Table 1. In another embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule includes a VH and/or VL domain encoded by a nucleic acid having a nucleotide sequence as set forth in Table 1, or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 9, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 9; and/or

a VL domain comprising the amino acid sequence of SEQ ID NO: 10, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence of SEQ ID NO: 10, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 10.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 9, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 9; and/or

a VL domain comprising the amino acid sequence of SEQ ID NO: 11, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence of SEQ ID NO: 11, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 11.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule is a full antibody or fragment thereof (e.g., a Fab, $F(ab')_2$, Fv, or a single chain Fv fragment (scFv)). In embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule is a monoclonal antibody or an antibody with single specificity. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, can also be a humanized, chimeric, camelid, shark, or an in vitro-generated antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, is a humanized antibody molecule. The heavy and light chains of the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, can be full-length (e.g., an antibody can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains) or can include an antigen-binding fragment (e.g., a Fab, F(ab')2, Fv, a single chain Fv fragment, a single domain antibody, a diabody (dAb), a bivalent antibody, or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, is in the form of a multispecific molecule, e.g., a bispecific molecule, e.g., as described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, has a heavy chain constant region (Fc) chosen from, e.g., the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. In some embodiments, the Fc region is chosen from the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In some embodiments, the Fc region is chosen from the heavy chain constant region of IgG1 or IgG2 (e.g., human IgG1, or IgG2). In some embodiments, the heavy chain constant region is human IgG1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule, has a light chain constant region chosen from, e.g., the light chain constant regions of kappa or lambda, preferably kappa (e.g., human kappa). In one embodiment, the constant region is altered, e.g., mutated, to modify the properties of the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule (e.g., to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function). For example, the constant region is mutated at positions 296 (M to Y), 298 (S to T), 300 (T to E), 477 (H to K) and 478 (N to F) to alter Fc receptor binding (e.g., the mutated positions correspond to positions 132 (M to Y), 134 (S to T), 136 (T to E), 313 (H to K) and 314 (N to F) of SEQ ID NOs: 212 or 214; or positions 135 (M to Y), 137 (S to T), 139 (T to E), 316 (H to K) and 317 (N to F) of SEQ ID NOs: 215, 216, 217 or 218), e.g., relative to human IgG1.

Antibody A-H.1 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 3278 and a light chain comprising the amino acid sequence of SEQ ID NO: 72. Antibody A-H.2 comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 3278 and a light chain comprising the amino acid sequence of SEQ ID NO: 3279.

TABLE 1

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

Antibody A (murine)			
SEQ ID NO: 3	HC CDR1 (Combined)	GYSFTTYYIH
SEQ ID NO: 4	HC CDR2 (Combined)	WFFPGSGNIKYNEKFKG
SEQ ID NO: 5	HC CDR3 (Combined)	SYYSYDVLDY
SEQ ID NO: 45	HC CDR1 (Kabat)	TYYIH
SEQ ID NO: 46	HC CDR2 (Kabat)	WFFPGSGNIKYNEKFKG
SEQ ID NO: 47	HC CDR3 (Kabat)	SYYSYDVLDY
SEQ ID NO: 48	HC CDR1 (Chothia)	GYSFTTY

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 49	HC CDR2 (Chothia)	FPGSGN
SEQ ID NO: 50	HC CDR3 (Chothia)	SYYSYDVLDY
SEQ ID NO: 1	VH	QVQLQQSGPELVKPGTSVKISCKASGYSFTTYY IHWVKQRPGQGLEWIGWFFPGSGNIKYNEKFKG KATLTADTSSSTAYMQLSSLTSEESAVYFCAGS YYSYDVLDYWGHGTTLTVSS
SEQ ID NO: 6	LC CDR1 (Combined)	KASQNVGINVV
SEQ ID NO: 7	LC CDR2 (Combined)	SSSHRYS
SEQ ID NO: 8	LC CDR3 (Combined)	QQFKSYPLT
SEQ ID NO: 51	LC CDR1 (Kabat)	KASQNVGINVV
SEQ ID NO: 52	LC CDR2 (Kabat)	SSSHRYS
SEQ ID NO: 53	LC CDR3 (Kabat)	QQFKSYPLT
SEQ ID NO: 54	LC CDR1 (Chothia)	KASQNVGINVV
SEQ ID NO: 55	LC CDR2 (chothia)	SSSHRYS
SEQ ID NO: 56	LC CDR3 (chothia)	QQFKSYPLT
SEQ ID NO: 2	VL	DILMTQSQKFMSTSLGDRVSVSCKASQNVGINV VWHQQKPGQSPKALIYSSSHRYSGVPDRFTGSG SGTDFTLTINNVQSEDLAEYFCQQFKSYPLTFG AGTKLELK

Antibody A humanized (A-H antibody)
A-H.1 antibody

SEQ ID NO: 3	HC CDR1 (Combined)	GYSFTTYYIH
SEQ ID NO: 4	HC CDR2 (Combined)	WFFPGSGNIKYNEKFKG
SEQ ID NO: 5	HC CDR3 (Combined)	SYYSYDVLDY
SEQ ID NO: 9	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
SEQ ID NO: 12	DNA VH	CAGGTGCAGCTGGTTCAGTCTGGCGCCGAAGTG AAGAAACCTGGCTCCTCCGTGAAGGTGTCCTGC AAGGCTTCCGGCTACTCCTTCACCACCTACTAC ATCCACTGGGTCCGACAGGCCCCTGGACAAGGA TTGGAATGGATGGGCTGGTTCTTCCCCGGCTCC GGCAACATCAAGTACAACGAGAAGTTCAAGGGC CGCGTGACCATCACCGCCGACACCTCTACCTCT ACCGCCTACATGGAACTGTCCAGCCTGAGATCT GAGGACACCGCCGTGTACTACTGCGCCGGCTCC TACTACTCTTACGACGTGCTGGATTACTGGGGC CAGGGCACCACAGTGACAGTGTCCTCT
SEQ ID NO: 69	VH-IgM constant delta CDC	METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKK PGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLE WMGWFFPGSGNIKYNEKFKGRVTITADTSTSTA YMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQG TTVTVSSGSASAPTLFPLVSCENSPSDTSSVAV GCLAQDFLPDSITFSWKYKNNSDISSTRGFPSV LRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQH PNGNKEKNVPLPVIAELPPKVSVFVPPRDGFFG NPRKSKLICQATGFSPRQIQVSWLREGKQVGSG VTTDQVQAEAKESGPTTYKVTSTLTIKESDWLG QSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRV FAIPPSFASIFLTKSTKLTCLVTDLTTYDSVTI SWTRQNGEAVKTHTNISESHPNATFSAVGEASI CEDDWNSGERFTCTVTHTDLASSLKQTISRPKG

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

		VALHRPDVYLLPPAREQLNLRESATITCLVTGF SPADVFVQWMQRGQPLSPEKYVTSAPMPEPQAP GRYFAHSILTVSEEEWNTGETYTCVVAHEALPN RVTERTVDKSTGKPTLYNVSLVMSDTAGTCY
SEQ ID NO: 70	VH-IgGA1	METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKK PGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLE WMGWFFPGSGNIKYNEKFKGRVTITADTSTSTA YMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQG TTVTVSSASPTSPKVFPLSLCSTQPDGNVVIAC LVQGFFPQEPLSVTWSESGQGVTARNFPPSQDA SGDLYTTSSQLTLPATQCLAGKSVTCHVKHYTN PSQDVTVPCPVPSTPPTPSPSTPPTPSPSCCHP RLSLHRPALEDLLLGSEANLTCTLTGLRDASGV TFTWTPSSGKSAVQGPPERDLCGCYSVSSVLPG CAEPWNHGKTFTCTAAYPESKTPLTATLSKSGN TFRPEVHLLPPPSEELALNELVTLTCLARGFSP KDVLVRWLQGSQELPREKYLTWASRQEPSQGTT TFAVTSILRVAAEDWKKGDTFSCMVGHEALPLA FTQKTIDRLAGKPTHVNVSVVMAEVDGTCY
SEQ ID NO: 71	VH-IgGA2	METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKK PGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLE WMGWFFPGSGNIKYNEKFKGRVTITADTSTSTA YMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQG TTVTVSSASPTSPKVFPLSLDSTPQDGNVVVAC LVQGFFPQEPLSVTWSESGQNVTARNFPPSQDA SGDLYTTSSQLTLPATQCPDGKSVTCHVKHYTN SSQDVTVPCRVPPPPPCCHPRLSLHRPALEDLL LGSEANLTCTLTGLRDASGATFTWTPSSGKSAV QGPPERDLCGCYSVSSVLPGCAQPWNHGETFTC TAAHPELKTPLTANITKSGNTFRPEVHLLPPPS EELALNELVTLTCLARGFSPKDVLVRWLQGSQE LPREKYLTWASRQEPSQGTTTYAVTSILRVAAE DWKKGETFSCMVGHEALPLAFTQKTIDRMAGKP THINVSVVMAEADGTCY
SEQ ID NO: 3278	Heavy chain	METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKK PGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLE WMGWFFPGSGNIKYNEKFKGRVTITADTSTSTA YMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQG TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO: 6	LC CDR1 (Combined)	KASQNVGINVV
SEQ ID NO: 7	LC CDR2 (Combined))	SSSHRYS
SEQ ID NO: 8	LC CDR3 (Combined)	QQFKSYPLT
SEQ ID NO: 10	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGINV VWHQQKPGKAPKALIYSSSHRYSGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 13	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTTCCTG TCCGCCTCTGTGGGCGACAGAGTGACCATCACA TGCAAGGCCTCTCAGAACGTGGGCATCAACGTC GTGTGGCACCAGCAGAAGCCTGGCAAGGCTCCT AAGGCTCTGATCTACTCCTCCAGCCACCGGTAC TCTGGCGTGCCCTCTAGATTTTCCGGCTCTGGC TCTGGCACCGAGTTTACCCTGACAATCTCCAGC CTGCAGCCTGAGGACTTCGCCACCTACTTTTGC

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

		CAGCAGTTCAAGAGCTACCCTCTGACCTTTGGC CAGGGCACCAAGCTGGAAATCAAG
SEQ ID NO: 72	VL and kappa constant region/light chain	METDTLLLWVLLLWVPGSTGDIQMTQSPSFLSA SVGDRVTITCKASQNVGINVVWHQQKPGKAPKA LIYSSSHRYSGVPSRFSGSGSGTEFTLTISSLQ PEDFATYFCQQFKSYPLTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC

A-H.2 antibody

SEQ ID NO: 3	HC CDR1 (Combined)	GYSFTTYYIH
SEQ ID NO: 4	HC CDR2 (Combined)	WFFPGSGNIKYNEKFKG
SEQ ID NO: 5	HC CDR3 (Combined)	SYYSYDVLDY
SEQ ID NO: 9	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
SEQ ID NO: 12	DNA VH	CAGGTGCAGCTGGTTCAGTCTGGCGCCGAAGTG AAGAAACCTGGCTCCTCCGTGAAGGTGTCCTGC AAGGCTTCCGGCTACTCCTTCACCACCTACTAC ATCCACTGGGTCCGACAGGCCCCTGGACAAGGA TTGGAATGGATGGGCTGGTTCTTCCCCGGCTCC GGCAACATCAAGTACAACGAGAAGTTCAAGGGC CGCGTGACCATCACCGCCGACACCTCTACCTCT ACCGCCTACATGGAACTGTCCAGCCTGAGATCT GAGGACACCGCCGTGTACTACTGCGCCGGCTCC TACTACTCTTACGACGTGCTGGATTACTGGGGC CAGGGCACCACAGTGACAGTGTCCTCT
SEQ ID NO: 3278	Heavy chain	METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKK PGSSVKVSCKASGYSFTTYYIHWVRQAPGQGLE WMGWFFPGSGNIKYNEKFKGRVTITADTSTSTA YMELSSLRSEDTAVYYCAGSYYSYDVLDYWGQG TTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT KVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFL FPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
SEQ ID NO: 6	LC CDR1 (Combined)	KASQNVGINVV
SEQ ID NO: 7	LC CDR2 (Combined))	SSSHRYS
SEQ ID NO: 8	LC CDR3 (Combined)	QQFKSYPLT
SEQ ID NO: 11	VL	DIQMTQSPSSLSASVGDRVTITCKASQNVGINV VWHQQKPGKVPKALIYSSSHRYSGVPSRFSGSG SGTDFTLTISSLQPEDVATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 14	DNA VL	GACATCCAGATGACCCAGTCTCCATCCTCTCTG TCCGCCTCTGTGGGCGACAGAGTGACCATCACA TGCAAGGCCTCTCAGAACGTGGGCATCAACGTC GTGTGGCACCAGCAGAAACCTGGCAAGGTGCCC AAGGCTCTGATCTACTCCTCCAGCCACAGATAC TCCGGCGTGCCCTCTAGATTCTCCGGCTCTGGC TCTGGCACCGACTTTACCCTGACAATCTCCAGC CTGCAGCCTGAGGACGTGGCCACCTACTTTTGC

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

		CAGCAGTTCAAGAGCTACCCTCTGACCTTTGGC CAGGGCACCAAGCTGGAAATCAAG
SEQ ID NO: 3279	Light chain	METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSA SVGDRVTITCKASQNVGINVVWHQQKPGKVPKA LIYSSSHRYSGVPSRFSGSGSGTDFTLTISSLQ PEDVATYFCQQFKSYPLTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK VQWKVDNALQSGNSQESVTEQDSKDSTYSLSST LTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR GEC
	A-H.3 antibody	
SEQ ID NO: 80	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 81	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 82	VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.4	
SEQ ID NO: 83	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 84	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 85	VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.5	
SEQ ID NO: 86	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFRDFY IHWVRQAPGQGLEWMGRVYPGSGSYRYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 87	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 88	VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFRDFY IHWVRQAPGQGLEWMGRVYPGSGSYRYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.6	
SEQ ID NO: 89	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 90	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 91	VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.7	
SEQ ID NO: 92	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVENKVAWHQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 93	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVENKV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 94	VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.8	
SEQ ID NO: 95	VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRIFAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 96	VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 97	VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRIFAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	A-H.9
SEQ ID NO: 98 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGNRVAWYQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 99 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGNRV AWYQQKPGKAPKALIYSSSHRYSGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 100 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.10
SEQ ID NO: 101 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRIFAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIKs
SEQ ID NO: 102 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 103 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRIFAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.11
SEQ ID NO: 104 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 105 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 106 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.12
SEQ ID NO: 107 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRVSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGNRVAWYQQKPGKAPKALIYSSSHRYKGVP

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 108 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 109 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRVSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.13	
SEQ ID NO: 110 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 111 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 112 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.14	
SEQ ID NO: 113 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 114 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 115 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.15	
SEQ ID NO: 116 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNKVAWHQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 117 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNKV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 118 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.16
SEQ ID NO: 119 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTY IHWVRQAPGQGLEWMGRVYPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 120 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 121 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTY IHWVRQAPGQGLEWMGRVYPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.17
SEQ ID NO: 122 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRIFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 123 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 124 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRIFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.18
SEQ ID NO: 125 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 126 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 127 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

A-H.19

SEQ ID NO: 128 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 129 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 130 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFRLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

A-H.20

SEQ ID NO: 131 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGGTFDKTY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 132 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 133 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFDKTY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

A-H.21

SEQ ID NO: 134 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 135 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 136 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

A-H.22

SEQ ID NO: 137 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNKVAWHQQKPGKAPKALIYSSSHRYKGVP

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 138 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNKV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 139 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.23	
SEQ ID NO: 140 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFRLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVADRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 141 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVADRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 142 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFRLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.24	
SEQ ID NO: 143 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNKVAWHQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 144 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNKV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 145 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.25	
SEQ ID NO: 146 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRVFAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDKVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 147 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDKV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 148 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRVFAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.26
SEQ ID NO: 149 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 150 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 151 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRIFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.27
SEQ ID NO: 153 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGNRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 154 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 155 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.28
SEQ ID NO: 156 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 157 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 158 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	A-H.29
SEQ ID NO: 159 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRISPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWHQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 160 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 161 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFHLWY IHWVRQAPGQGLEWMGRISPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.31
SEQ ID NO: 162 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 163 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 164 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.31
SEQ ID NO: 165 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFHLWY IHWVRQAPGQGLEWMGRVFAGSGSYRYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 166 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 167 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFHLWY IHWVRQAPGQGLEWMGRVFAGSGSYRYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.32
SEQ ID NO: 168 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVADRVAWYQQKPGKAPKALIYSSSHRYKGVP

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 169 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVADRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 170 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.33
SEQ ID NO: 171 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 172 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 173 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.34
SEQ ID NO: 174 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRISPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGNRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 175 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 176 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFRLTY IHWVRQAPGQGLEWMGRISPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.35
SEQ ID NO: 177 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 178 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 179 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.36
SEQ ID NO: 180 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVEDRVAWHQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 181 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVEDRV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 182 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFKLTY IHWVRQAPGQGLEWMGRVSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.37
SEQ ID NO: 183 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTY IHWVRQAPGQGLEWMGRIYPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVADRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 184 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVADRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 185 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKTY IHWVRQAPGQGLEWMGRIYPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.38
SEQ ID NO: 186 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 187 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 188 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKTY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	A-H.39
SEQ ID NO: 189 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 190 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 191 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.40
SEQ ID NO: 192 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 193 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVGDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 194 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKIY IHWVRQAPGQGLEWMGRISAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.41
SEQ ID NO: 195 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGGTFKLTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDDRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 196 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDDRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 197 VH	QVQLVQSGAEVKKPGSSVKVSCKASGGTFKLTY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
	A-H.42
SEQ ID NO: 198 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNRVAWHQQKPGKAPKALIYSSSHRYKGVP

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 199 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNRV AWHQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 200 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFKLTY IHWVRQAPGQGLEWMGRISPGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.43	
SEQ ID NO: 201 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVDNRVAWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 202 VL	DIQMTQSPSFLSASVGDRVTITCKASQNVDNRV AWYQQKPGKAPKALIYSSSHRYKGVPSRFSGSG SGTEFTLTISSLQPEDFATYFCQQFKSYPLTFG QGTKLEIK
SEQ ID NO: 203 VH	QVQLVQSGAEVKKPGSSVKVSCKASGHDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.44	
SEQ ID NO: 204 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGDRVVWYQQKPGKAPKALIYSSSHRYKGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 205 VH	QVQLVQSGAEVKKPGSSVKVSCKASGTDFDKFY IHWVRQAPGQGLEWMGRVSAGSGNVKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.45	
SEQ ID NO: 206 VH + VL	QVOLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAVS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 207 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAVS YYSYDVLDYWGQGTTVTVSS
A-H.46	
SEQ ID NO: 208 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

	GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 209 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSAGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.47	
SEQ ID NO: 210 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 211 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.48	
SEQ ID NO: 212 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAVS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 213 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAVS YYSYDVLDYWGQGTTVTVSS
A-H.49	
SEQ ID NO: 214 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSPGSGNTKYNEKFKG RVITIADTSTSIAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFA1YFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 215 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFSPGSGNTKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.50	
SEQ ID NO: 216 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGRIFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK

TABLE 1-continued

Amino acid and nucleotide sequences for murine, chimeric and humanized antibody molecules. The antibody molecules include murine mAb Antibody A, and humanized mAb Antibody A-H Clones A-H.1 and A-H.2. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

SEQ ID NO: 217 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGRIFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.51	
SEQ ID NO: 218 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS IYSAGVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 219 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS IYSAGVLDYWGQGTTVTVSS
A-H.52	
SEQ ID NO: 220 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTLGY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 221 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFTLGY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.53	
SEQ ID NO: 222 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFRLTY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVnTCKASQ NVGINVVWHQQKPGKAPKALIYSSSHRYSGVPS RFSGSGSGTEFTLTISSLQPEDFATYFGQQFKS YPLTFGQGTKLEIK
SEQ ID NO: 223 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFRLTY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS
A-H.54	
SEQ ID NO: 224 VH + VL	QVQLVQSGAEVKKPGSSVKVSCKASGYSFHNWY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGG GSGGGGSDIQMTQSPSFLSASVGDRVTITCKAS QNVGINVVWHQQKPGKAPKALIYSSSHRYSGVP SRFSGSGSGTEFTLTISSLQPEDFATYFCQQFK SYPLTFGQGTKLEIK
SEQ ID NO: 225 VH	QVQLVQSGAEVKKPGSSVKVSCKASGYSFHNWY IHWVRQAPGQGLEWMGWFFPGSGNIKYNEKFKG RVTITADTSTSTAYMELSSLRSEDTAVYYCAGS YYSYDVLDYWGQGTTVTVSS

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises a VH and/or a VL of an antibody described in Table 1, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule comprises a VH and a VL of an antibody described in Table 1, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, an anti-TCRβV antibody disclosed herein has an antigen binding domain having a VL having a consensus sequence of SEQ ID NO: 230, wherein position 30 is G, E, A or D; position 31 is N or D; position 32 is R or K; position 36 is Y or H; and/or position 56 is K or S.

In some embodiments, an anti-TCRβV antibody disclosed herein has an antigen binding domain having a VH having a consensus sequence of SEQ ID NO: 231, wherein: position 27 is H or T or G or Y; position 28 is D or T or S; position 30 is H or R or D or K or T; position 31 is L or D or K or T or N; position 32 is W or F or T or I or Y or G; position 49 is R or W; position 50 is V or I or F; position 51 is F or S or Y; position 52 is A or P; position 56 is N or S; position 57 is T or V or Y or I; position 58 is K or R; position 97 is G or V; position 99 is Y or I; position 102 is Y or A; and/or position 103 is D or G.

Anti-TCRβV12 Antibodies

Accordingly, in one aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to human TCRβV12, e.g., a TCRβV12 subfamily comprising: TCRβV12-4*01, TCRβV12-3*01 or TCRβV12-5*01. In some embodiments the TCRβV12 subfamily comprises TCRβV12-4*01. In some embodiments the TCRβV12 subfamily comprises TCRβV12-3*01.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, is a non-murine antibody molecule, e.g., a human or humanized antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule is a human antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule is a humanized antibody molecule.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, is isolated or recombinant.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises at least one antigen-binding region, e.g., a variable region or an antigen-binding fragment thereof, from an antibody described herein, e.g., an antibody described in Table 2, or encoded by a nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises at least one, two, three or four variable regions from an antibody described herein, e.g., an antibody as described in Table 2, or encoded by a nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises at least one or two heavy chain variable regions from an antibody described herein, e.g., an antibody as described in Table 2, or encoded by a nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises at least one or two light chain variable regions from an antibody described herein, e.g., an antibody as described in Table 2, or encoded by a nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises a heavy chain constant region for an IgG4, e.g., a human IgG4. In still another embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes a heavy chain constant region for an IgG1, e.g., a human IgG1. In one embodiment, the heavy chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes a kappa light chain constant region, e.g., a human kappa light chain constant region. In one embodiment, the light chain constant region comprises an amino sequence set forth in Table 3, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes at least one, two, or three complementarity determining regions (CDRs) from a heavy chain variable region of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes at least one, two, or three CDRs (or collectively all of the CDRs) from a heavy chain variable region comprising an amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes at least one, two, or three complementarity determining regions (CDRs) from a light chain variable region of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes at least one, two, or three CDRs (or collectively all of the CDRs) from a light chain variable region comprising an amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g.,

amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, includes at least one, two, three, four, five or six CDRs (or collectively all of the CDRs) from a heavy and light chain variable region comprising an amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2. In one embodiment, one or more of the CDRs (or collectively all of the CDRs) have one, two, three, four, five, six or more changes, e.g., amino acid substitutions or deletions, relative to the amino acid sequence shown in Table 2, or encoded by a nucleotide sequence shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, molecule includes all six CDRs from an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2, or closely related CDRs, e.g., CDRs which are identical or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions). In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to Kabat et al. (e.g., at least one, two, or three CDRs according to the Kabat definition as set out in Table 2) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to Kabat et al. (e.g., at least one, two, or three CDRs according to the Kabat definition as set out in Table 2) from a light chain variable region of an antibody described herein, e.g., an antibody as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Kabat et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Kabat et al. (e.g., at least one, two, three, four, five, or six CDRs according to the Kabat definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Kabat et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes all six CDRs according to Kabat et al. (e.g., all six CDRs according to the Kabat definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to Kabat et al. shown in Table 2. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three hypervariable loops that have the same canonical structures as the corresponding hypervariable loop of an antibody described herein, e.g., an antibody described in Table 2, e.g., the same canonical structures as at least loop 1 and/or loop 2 of the heavy and/or light chain variable domains of an antibody described herein. See, e.g., Chothia et al., (1992) J. Mol. Biol. 227:799-817; Tomlinson et al., (1992) J. Mol. Biol. 227:776-798 for descriptions of hypervariable loop canonical structures. These structures can be determined by inspection of the tables described in these references.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to Chothia et al. (e.g., at least one, two, or three CDRs according to the Chothia definition as set out in Table 2) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Chothia et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to Chothia et al. (e.g., at least one, two, or three CDRs according to the Chothia definition as set out in Table 2) from a light chain variable region of an antibody described herein, e.g., an antibody as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to Chothia et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, three, four, five, or six CDRs according to Chothia et al. (e.g., at least one, two, three, four, five, or six CDRs according to the Chothia definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in

Table 2, or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to Chothia et al. shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes all six CDRs according to Chothia et al. (e.g., all six CDRs according to the Chothia definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to Chothia et al. shown in Table 2. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule may include any CDR described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to a combined CDR (e.g., at least one, two, or three CDRs according to the combined CDR definition as set out in Table 2) from a heavy chain variable region of an antibody described herein, e.g., an antibody chosen as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to combined CDR shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, or three CDRs according to a combined CDR (e.g., at least one, two, or three CDRs according to the combined CDR definition as set out in Table 2) from a light chain variable region of an antibody described herein, e.g., an antibody as described in Table 2, or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, or three CDRs according to a combined CDR shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes at least one, two, three, four, five, or six CDRs according to a combined CDR. (e.g., at least one, two, three, four, five, or six CDRs according to the combined CDR definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to one, two, three, four, five, or six CDRs according to a combined CDR shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes all six CDRs according to a combined CDR (e.g., all six CDRs according to the combined CDR definition as set out in Table 2) from the heavy and light chain variable regions of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or encoded by the nucleotide sequence in Table 2; or a sequence substantially identical (e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical) to any of the aforesaid sequences; or which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) relative to all six CDRs according to a combined CDR shown in Table 2. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule may include any CDR described herein.

In some embodiments, a combined CDR as set out in Table 1 is a CDR that comprises a Kabat CDR and a Chothia CDR.

In some embodiments, the anti-TCRβV antibody molecule, e e.g., anti-TCRβV12 antibody molecule, molecule includes a combination of CDRs or hypervariable loops identified as combined CDRs in Table 1. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, can contain any combination of CDRs or hypervariable loops according the "combined" CDRs are described in Table 1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes a combination of CDRs or hypervariable loops defined according to the Kabat et al. and Chothia et al., or as described in Table 1

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule can contain any combination of CDRs or hypervariable loops according to the Kabat and Chothia definitions.

In an embodiment, e.g., an embodiment comprising a variable region, a CDR (e.g., a combined CDR, Chothia CDR or Kabat CDR), or other sequence referred to herein, e.g., in Table 2, the antibody molecule is a monospecific antibody molecule, a bispecific antibody molecule, a bivalent antibody molecule, a biparatopic antibody molecule, or an antibody molecule that comprises an antigen binding fragment of an antibody, e.g., a half antibody or antigen binding fragment of a half antibody. In certain embodiments the antibody molecule comprises a multispecific molecule, e.g., a bispecific molecule, e.g., as described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes:

(i) one, two or all of a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 16, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO: 30, and/or

(ii) one, two or all of a heavy chain complementarity determining region 1 (HC CDR1), heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 15, SEQ ID NO: 23, SEQ ID NO: 24 or SEQ ID NO: 25.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 20, a LC CDR2 amino acid sequence of SEQ ID NO: 21, or a LC CDR3 amino acid sequence of SEQ ID NO: 22; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 17, a HC CDR2 amino acid sequence of SEQ ID NO: 18, or a HC CDR3 amino acid sequence of SEQ ID NO: 19.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 20, a LC CDR2 amino acid sequence of SEQ ID NO: 21, and a LC CDR3 amino acid sequence of SEQ ID NO: 2; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 17, a HC CDR2 amino acid sequence of SEQ ID NO: 18, and a HC CDR3 amino acid sequence of SEQ ID NO: 19.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 63, a LC CDR2 amino acid sequence of SEQ ID NO: 64, or a LC CDR3 amino acid sequence of SEQ ID NO: 65; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 57, a HC CDR2 amino acid sequence of SEQ ID NO: 58, or a HC CDR3 amino acid sequence of SEQ ID NO: 59.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 63, a LC CDR2 amino acid sequence of SEQ ID NO: 64, or a LC CDR3 amino acid sequence of SEQ ID NO: 65; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 57, a HC CDR2 amino acid sequence of SEQ ID NO: 58, or a HC CDR3 amino acid sequence of SEQ ID NO: 59.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a LC CDR1 amino acid sequence of SEQ ID NO: 66, a LC CDR2 amino acid sequence of SEQ ID NO: 67, or a LC CDR3 amino acid sequence of SEQ ID NO: 68; and/or

(ii) a HC CDR1 amino acid sequence of SEQ ID NO: 60, a HC CDR2 amino acid sequence of SEQ ID NO: 61, or a HC CDR3 amino acid sequence of SEQ ID NO: 62.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

(i) a light chain variable region (VL) comprising a LC CDR1 amino acid sequence of SEQ ID NO: 63, a LC CDR2 amino acid sequence of SEQ ID NO: 64, or a LC CDR3 amino acid sequence of SEQ ID NO: 65; and/or

(ii) a heavy chain variable region (VH) comprising a HC CDR1 amino acid sequence of SEQ ID NO: 57, a HC CDR2 amino acid sequence of SEQ ID NO: 58, or a HC CDR3 amino acid sequence of SEQ ID NO: 59.

In one embodiment, the light or the heavy chain variable framework (e.g., the region encompassing at least FR1, FR2, FR3, and optionally FR4) of the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule can be chosen from: (a) a light or heavy chain variable framework including at least 80%, 85%, 87% 90%, 92%, 93%, 95%, 97%, 98%, or 100% of the amino acid residues from a human light or heavy chain variable framework, e.g., a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (b) a light or heavy chain variable framework including from 20% to 80%, 40% to 60%, 60% to 90%, or 70% to 95% of the amino acid residues from a human light or heavy chain variable framework, e.g., a light or heavy chain variable framework residue from a human mature antibody, a human germline sequence, or a human consensus sequence; (c) a non-human framework (e.g., a rodent framework); or (d) a non-human framework that has been modified, e.g., to remove antigenic or cytotoxic determinants, e.g., deimmunized, or partially humanized. In one embodiment, the light or heavy chain variable framework region (particularly FR1, FR2 and/or FR3) includes a light or heavy chain variable framework sequence at least 70, 75, 80, 85, 87, 88, 90, 92, 94, 95, 96, 97, 98, 99% identical or identical to the frameworks of a VL or VH segment of a human germline gene.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, comprises a heavy chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more changes, e.g., amino acid substitutions or deletions, from an amino acid sequence described in Table 2. e.g., the amino acid sequence of the FR region in the entire variable region, e.g., shown in FIGS. **2**A and **2**B, or in SEQ ID NOs: 23-25.

Alternatively, or in combination with the heavy chain substitutions described herein the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain variable domain having at least one, two, three, four, five, six, seven, ten, fifteen, twenty or more amino acid changes, e.g., amino acid substitutions or deletions, from an amino acid sequence of an antibody described herein. e.g., the amino acid sequence of the FR region in the entire variable region, e.g., shown in FIGS. **2**A and **2**B, or in SEQ ID NOs: 26-30.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes one, two, three, or four heavy chain framework regions shown in FIG. **2**A, or a sequence substantially identical thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes one, two, three, or four light chain framework regions shown in FIG. **2**B, or a sequence substantially identical thereto.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the light chain framework region 1 e.g., as shown in FIG. **2**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the light chain framework region 2 e.g., as shown in FIG. **2**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the light chain framework region 3, e.g., as shown in FIG. **2**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the light chain framework region 4, e.g., as shown in FIG. **2**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more, e.g., all, position disclosed herein according to Kabat numbering. In some embodiments, FR1 comprises an Aspartic Acid at position 1, e.g., a substitution at position 1 according to Kabat numbering, e.g., an Alanine to Aspartic Acid substitution. In some embodiments, FR1 comprises an Asparagine at position 2, e.g., a substitution at position 2 according to Kabat numbering, e.g., an Isoleucine to Asparagine substi-

tution, Serine to Asparagine substitution or Tyrosine to Asparagine substitution. In some embodiments, FR1 comprises a Leucine at position 4, e.g., a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a substitution at position 1 according to Kabat numbering, e.g., an Alanine to Aspartic Acid substitution, a substitution at position 2 according to Kabat numbering, e.g., an Isoleucine to Asparagine substitution, Serine to Asparagine substitution or Tyrosine to Asparagine substitution, and a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a substitution at position 1 according to Kabat numbering, e.g., an Alanine to Aspartic Acid substitution, and a substitution at position 2 according to Kabat numbering, e.g., an Isoleucine to Asparagine substitution, Serine to Asparagine substitution or Tyrosine to Asparagine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a substitution at position 1 according to Kabat numbering, e.g., an Alanine to Aspartic Acid substitution, and a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a substitution at position 2 according to Kabat numbering, e.g., an Isoleucine to Asparagine substitution, Serine to Asparagine substitution or Tyrosine to Asparagine substitution, and a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more, e.g., all, position disclosed herein according to Kabat numbering. In some embodiments, FR3 comprises a Glycine at position 66, e.g., a substitution at position 66 according to Kabat numbering, e.g., a Lysine to Glycine substitution, or a Serine to Glycine substitution. In some embodiments, FR3 comprises an Asparagine at position 69, e.g., a substitution at position 69 according to Kabat numbering, e.g., a Tyrosine to Asparagine substitution. In some embodiments, FR3 comprises a Tyrosine at position 71, e.g., a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, or an Alanine to Tyrosine substitution.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a substitution at position 66 according to Kabat numbering, e.g., a Lysine to Glycine substitution, or a Serine to Glycine substitution, and a substitution at position 69 according to Kabat numbering, e.g., a Tyrosine to Asparagine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a substitution at position 66 according to Kabat numbering, e.g., Lysine to Glycine substitution, or a Serine to Glycine substitution, and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, or an Alanine to Tyrosine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a substitution at position 69 according to Kabat numbering, e.g., a Tyrosine to Asparagine substitution and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, or an Alanine to Tyrosine substitution. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a substitution at position 66 according to Kabat numbering, e.g., a Lysine to Glycine substitution, or a Serine to Glycine substitution, a substitution at position 69 according to Kabat numbering, e.g., a Tyrosine to Asparagine substitution and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, or an Alanine to Tyrosine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising: a framework region 1 (FR1) comprising a substitution at position 2 according to Kabat numbering, e.g., a Isoleucine to Asparagine substitution; and a framework region 3 (FR3), comprising a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 26. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising: (a) a framework region 1 (FR1) comprising a substitution at position 1 according to Kabat numbering, e.g., a Alanine to Aspartic Acid substitution, and a substitution at position 2 according to Kabat numbering, e.g., a Isoleucine to Asparagine substitution; and (b) a framework region 3 (FR3), comprising a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 27 In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising: (a) a framework region 1 (FR1) comprising a substitution at position 2 according to Kabat numbering, e.g., a Serine to Asparagine substitution; and a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution; and (b) a framework region 3 (FR3), comprising a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution and a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, e.g., as shown in the amino acid

sequence of SEQ ID NO: 28 In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising: (a) a framework region 1 (FR1) comprising a substitution at position 2 according to Kabat numbering, e.g., a Serine to Asparagine substitution; and (b) a framework region 3 (FR3) comprising a substitution at position 66 according to Kabat numbering, e.g., a Lysine to Glycine substitution; a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution; and a substitution at position 71 according to Kabat numbering, e.g., a Alanine to Tyrosine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 29. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain comprising: (a) a framework region 1 (FR1) comprising a substitution at position 2 according to Kabat numbering, e.g., a Tyrosine to Asparagine substitution; and (b) a framework region 3 (FR3) comprising a substitution at position 66 according to Kabat numbering, e.g., a Serine to Glycine substitution; a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution; and a substitution at position 71 according to Kabat numbering, e.g., a Alanine to Tyrosine substitution, e.g., as shown in the amino acid sequence of SEQ ID NO: 29. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises a light chain variable domain comprising: (a) a framework region 1 (FR1) comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more (e.g., all) positions disclosed herein according to Kabat numbering, and (b) a framework region 3 (FR3) comprising a change, e.g., a substitution (e.g., a conservative substitution) at one or more (e.g., all) position disclosed herein according to Kabat numbering. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework region 1, e.g., as shown in FIG. **2**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework region 2, e.g., as shown in FIG. **2**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework region 3, e.g., as shown in FIG. **2**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework region 4, e.g., as shown in FIG. **2**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework regions 1-4, e.g., SEQ ID NOS: 20-23, or as shown in FIG. **2**A.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the light chain framework regions 1-4, e.g., SEQ ID NOs: 26-30, or as shown in FIG. **2**B.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises the heavy chain framework regions 1-4, e.g., SEQ ID NOs: 23-25; and the light chain framework regions 1-4, e.g., SEQ ID NOs: 26-30, or as shown in FIGS. **2**A and **2**B.

In some embodiments, the heavy or light chain variable domain, or both, of, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes an amino acid sequence, which is substantially identical to an amino acid disclosed herein, e.g., at least 80%, 85%, 90%, 92%, 95%, 97%, 98%, 99% or higher identical to a variable region of an antibody described herein, e.g., an antibody as described in Table 2, or encoded by the nucleotide sequence in Table 2; or which differs at least 1 or 5 residues, but less than 40, 30, 20, or 10 residues, from a variable region of an antibody described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises at least one, two, three, or four antigen-binding regions, e.g., variable regions, having an amino acid sequence as set forth in Table 2, or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the sequences shown in Table 2. In another embodiment, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule includes a VH and/or VL domain encoded by a nucleic acid having a nucleotide sequence as set forth in Table 2, or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in Table 2.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

- a VH domain comprising an amino acid sequence chosen from the amino acid sequence of SEQ ID NO: 23, SEQ ID NO:24 or SEQ ID NO:25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, SEQ ID NO:24 or SEQ ID NO:25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23, SEQ ID NO:24 or SEQ ID NO:25; and/or
- a VL domain comprising an amino acid sequence chosen from the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO: 30.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

- a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and
- a VL domain comprising the amino acid sequence of SEQ ID NO: 26, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 26, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 27, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 27, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 28, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 28, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 23, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 23, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 23; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 26, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 26, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 27, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 27, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 28, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 28, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 24, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 24, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid

sequence SEQ ID NO: 24, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 24; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 26, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 26, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 26.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 27, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 27, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 27.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 28, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 28, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 28.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 29, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 29, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 29.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule comprises:

a VH domain comprising the amino acid sequence of SEQ ID NO: 25, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 25, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 25; and

a VL domain comprising the amino acid sequence of SEQ ID NO: 30, an amino acid sequence at least about 85%, 90%, 95%, 99% or more identical to the amino acid sequence SEQ ID NO: 30, or an amino acid sequence which differs by no more than 1, 2, 5, 10, or 15 amino acid residues from the amino acid sequence of SEQ ID NO: 30.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule is a full antibody or fragment thereof (e.g., a Fab, F(ab')2, Fv, or a single chain Fv fragment (scFv)). In embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV6 (e.g., anti-TCRβV6-5*01) antibody molecule is a monoclonal antibody or an antibody with single specificity. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule, can also be a humanized, chimeric, camelid, shark, or an in vitro-generated antibody molecule. In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule is a humanized antibody molecule. The heavy and light chains of the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule can be full-length (e.g., an antibody can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains) or can include an antigen-binding fragment (e.g., a Fab, F(ab')2, Fv, a single chain Fv fragment, a single domain antibody, a diabody (dAb), a bivalent antibody, or bispecific antibody or fragment thereof, a single domain variant thereof, or a camelid antibody).

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule is in the form of a multispecific molecule, e.g., a bispecific molecule, e.g., as described herein.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule has a heavy chain constant region (Fc) chosen from, e.g., the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. In some embodiments, the Fc region is chosen from the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In some embodiments, the Fc region is chosen from the heavy chain constant region of IgG1 or IgG2 (e.g., human IgG1, or IgG2). In some embodiments, the heavy chain constant region is human IgG1.

In some embodiments, the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule has a light chain constant region chosen from, e.g., the light chain constant regions of kappa or lambda, preferably kappa (e.g., human kappa). In one embodiment, the constant region is

altered, e.g., mutated, to modify the properties of the anti-TCRβV antibody molecule, e.g., anti-TCRβV12 antibody molecule (e.g., to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function). For example, the constant region is mutated at positions 296 (M to Y), 298 (S to T), 300 (T to E), 477 (H to K) and 478 (N to F) to alter Fc receptor binding (e.g., the mutated positions correspond to positions 132 (M to Y), 134 (S to T), 136 (T to E), 313 (H to K) and 314 (N to F) of SEQ ID NOs: 212 or 214; or positions 135 (M to Y), 137 (S to T), 139 (T to E), 316 (H to K) and 317 (N to F) of SEQ ID NOs: 215, 216, 217 or 218).

Antibody B-H.1 comprises a first chain comprising the amino acid sequence of SEQ ID NO: 3280 and a second chain comprising the amino acid sequence of SEQ ID NO: 3281.

TABLE 2

Amino acid and nucleotide sequences for murine and humanized antibody molecules. The antibody molecules include murine mAb Antibody B and humanized mAb Antibody B-H.1. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

Antibody B (murine)		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 57	HC CDR1 (Kabat)	NFGMH
SEQ ID NO: 58	HC CDR2 (Kabat)	YISSGSSTIYYADTLKG
SEQ ID NO: 59	HC CDR3 (Kabat)	RGEGAMDY
SEQ ID NO: 60	HC CDR1 (Chothia)	GFTFSNF
SEQ ID NO: 61	HC CDR2 (Chothia)	SSGSST
SEQ ID NO: 62	HC CDR3 (Chothia)	RGEGAMDY
SEQ ID NO: 15	VH	DVQLVESGGGLVQPGGSRKLSCAASGFTFSNFGM HWVRQAPDKGLEWVAYISSGSSTIYYADTLKGRF TISRDNPKNTLFLQMTSLRSEDTAMYYCARRGEGA MDYWGQGTSVTVSS
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 63	LC CDR1 (Kabat)	RASSSVNYIY
SEQ ID NO: 64	LC CDR2 (Kabat)	YTSNLAP
SEQ ID NO: 65	LC CDR3 (Kabat)	QQFTSSPFT
SEQ ID NO: 66	LC CDR1 (Chothia)	RASSSVNYIY
SEQ ID NO: 67	LC CDR2 (Chothia)	YTSNLAP
SEQ ID NO: 68	LC CDR3 (Chothia)	QQFTSSPFT
SEQ ID NO: 16	VL	ENVLTQSPAIMSASLGEKVTMSCRASSSVNYIYWY QQKSDASPKLWIYYTSNLAPGVPTRFSGSGSGNSY SLTISSMEGEDAATYYCQQFTSSPFTFGSGTKLEIK
Antibody B humanized (B-H)		
Antibody B-H.1A HC-1		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 3438	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFGMH WVRQAPGKGLEWVSYISSGSSTIYYADTLKGRFTI SRDNAKNSLYLQMNSLRAEDTAVYYCARRGEGA MDYWGQGTTVTVSS
SEQ ID NO: 31	DNA VH	GAGGTGCAGCTGGTTGAATCTGGCGGAGGATTG GTTCAGCCTGGCGGCTCTCTGAGACTGTCTTGTG CCGCTTCTGGCTTCACCTTCTCCAACTTCGGCAT GCACTGGGTCCGACAGGCCCCTGGAAAAGGACT GGAATGGGTGTCCTACATCTCCTCCGGCTCCTCC ACCATCTACTACGCTGACACCCTGAAGGGCAGA TTCACCATCTCTCGGGACAACGCCAAGAACTCCC TGTACCTGCAGATGAACAGCCTGAGAGCCGAGG ACACCGCCGTGTACTACTGTGCTAGAAGAGGCG AGGGCGCCATGGATTATTGGGGCCAGGGAACCA CAGTGACCGTGTCTAGC
Antibody B-H.1B HC-2		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 24	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFGMH WVRQAPGKGLEWVSYISSGSSTIYYADTLKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARRGEGA MDYWGQGTTVTVSS
SEQ ID NO: 32	DNA VH	GAGGTGCAGCTGGTTGAATCTGGCGGAGGATTG GTTCAGCCTGGCGGCTCTCTGAGACTGTCTTGTG CCGCTTCTGGCTTCACCTTCTCCAACTTCGGCAT GCACTGGGTCCGACAGGCCCCTGGAAAAGGACT GGAATGGGTGTCCTACATCTCCTCCGGCTCCTCC

TABLE 2-continued

Amino acid and nucleotide sequences for murine and humanized antibody molecules. The antibody molecules include murine mAb Antibody B and humanized mAb Antibody B-H.1. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

		ACCATCTACTACGCTGACACCCTGAAGGGCAGA
		TTCACCATCAGCCGGGACAACTCCAAGAACACC
		CTGTACCTGCAGATGAACTCCCTGAGAGCCGAG
		GACACCGCCGTGTACTACTGTGCTAGAAGAGGC
		GAGGGCGCCATGGATTATTGGGGCCAGGGAACC
		ACAGTGACCGTGTCTAGC
Antibody B-H.1C HC-3		
SEQ ID NO: 17	HC CDR1 (Combined)	GFTFSNFGMH
SEQ ID NO: 18	HC CDR2 (Combined)	YISSGSSTIYYADTLKG
SEQ ID NO: 19	HC CDR3 (Combined)	RGEGAMDY
SEQ ID NO: 25	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSNFGM
		HWVRQAPGKGLEWVAYISSGSSTIYYADTLKGRF
		TISRDNSKNTLYLQMNSLRAEDTAVYYCARRGEG
		AMDYWGQGTTVTVSS
SEQ ID NO: 33	DNA VH	CAGGTGCAGCTGGTGGAATCTGGTGGCGGAGTT
		GTGCAGCCTGGCAGATCCCTGAGACTGTCTTGTG
		CCGCCTCTGGCTTCACCTTCTCCAACTTCGGCAT
		GCACTGGGTCCGACAGGCCCCTGGAAAAGGATT
		GGAGTGGGTCGCCTACATCTCCTCCGGCTCCTCC
		ACCATCTACTACGCTGACACCCTGAAGGGCAGA
		TTCACCATCAGCCGGGACAACTCCAAGAACACC
		CTGTACCTGCAGATGAACTCCCTGAGAGCCGAG
		GACACCGCCGTGTACTACTGTGCTAGAAGAGGC
		GAGGGCGCCATGGATTATTGGGGCCAGGGAACC
		ACAGTGACCGTGTCTAGC
Antibody B-H.1D LC-1		
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 26	VL	DNQLTQSPSFLSASVGDRVTITCRASSSVNYIYWY
		QQKPGKAPKLLIYYTSNLAPGVPSRFSGSGSGNEY
		TLTISSLQPEDFATYYCQQFTSSPFTFGQGTKLEIK
SEQ ID NO: 34	DNA VL	GATAACCAGCTGACCCAGTCTCCTAGCTTCCTGT
		CTGCCTCTGTGGGCGACAGAGTGACAATTACCT
		GCCGGGCCTCCTCCTCCGTGAACTACATCTACTG
		GTATCAGCAGAAGCCCGGCAAGGCCCCTAAGCT
		GCTGATCTACTACACCTCCAATCTGGCCCCTGGC
		GTGCCCTCTAGATTTTCCGGATCTGGCTCCGGCA
		ACGAGTATACCCTGACAATCTCCAGCCTGCAGC
		CTGAGGACTTCGCCACCTACTACTGCCAGCAGTT
		CACCTCCTCTCCATTCACCTTTGGCCAGGGCACC
		AAGCTGGAAATCAAA
Antibody B-H.1E LC-2		
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 27	VL	DNQLTQSPSSLSASVGDRVTITCRASSSVNYIYWY
		QQKPGKAPKLLIYYTSNLAPGVPSRFSGSGSGNDY
		TLTISSLQPEDFATYYCQQFTSSPFTFGQGTKLEIK
SEQ ID NO: 35	DNA VL	ATAACCAGCTGACCCAGTCTCCTTCCAGCCTGTC
		TGCTTCTGTGGGCGACAGAGTGACAATTACCTGC
		CGGGCCTCCTCCTCCGTGAACTACATCTACTGGT
		ATCAGCAGAAGCCCGGCAAGGCCCCTAAGCTGC
		TGATCTACTACACCTCCAATCTGGCCCCTGGCGT
		GCCCTCTAGATTTTCCGGATCTGGCTCCGGCAAC
		GACTATACCCTGACAATCTCCAGCCTGCAGCCTG
		AGGACTTCGCCACCTACTACTGCCAGCAGTTCAC
		CTCCTCTCCATTCACCTTTGGCCAGGGCACCAAG
		CTGGAAATCAAA
Antibody B-H.1F LC-3		
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 28	VL	ENVLTQSPATLSVSPGERATLSCRASSSVNYIYWY
		QQKPGQAPRLLIYYTSNLAPGIPARFSGSGSGNEYT
		LTISSLQSEDFAVYYCQQFTSSPFTFGQGTKLEIK
SEQ ID NO: 36	DNA VL	GAGAATGTGCTGACCCAGTCTCCTGCCACACTGT
		CTGTTAGCCCTGGCGAGAGAGCTACCCTGAGCT
		GCAGAGCCTCTTCCTCCGTGAACTACATCTACTG
		GTATCAGCAGAAGCCCGGCCAGGCTCCTAGACT
		GCTGATCTACTACACCTCCAATCTGGCCCCTGGC

TABLE 2-continued

Amino acid and nucleotide sequences for murine and humanized antibody molecules. The antibody molecules include murine mAb Antibody B and humanized mAb Antibody B-H.1. The amino acid the heavy and light chain CDRs, and the amino acid and nucleotide sequences of the heavy and light chain variable regions, and the heavy and light chains are shown.

		ATCCCTGCCAGATTTTCCGGATCTGGCTCCGGCA
		ACGAGTATACCCTGACCATCTCCAGCCTGCAGTC
		CGAGGACTTTGCTGTGTACTATTGCCAGCAGTTC
		ACAAGCAGCCCTTTCACCTTTGGCCAGGGCACC
		AAGCTGGAAATCAAA
Antibody B-H.1G LC-4		
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 29	VL	QNVLTQPPSASGTPGQRVTISCRASSSVNYIYWYQ
		QLPGTAPKLLIYYTSNLAPGVPDRFSGSGSGNSYSL
		AISGLRSEDEADYYCQQFTSSPFTFGTGTKVTVL
SEQ ID NO: 37	DNA VL	CAGAATGTGCTGACCCAACCTCCTTCCGCCTCTG
		GCACACCTGGACAGAGAGTGACAATCTCCTGCC
		GGGCCTCCTCCTCCGTGAACTACATCTACTGGTA
		TCAGCAGCTGCCCGGCACCGCTCCTAAACTGCTG
		ATCTACTACACCTCCAATCTGGCCCCTGGCGTGC
		CCGATAGATTTTCCGGATCTGGCTCCGGCAACTC
		CTACAGCCTGGCTATCTCTGGCCTGAGATCTGAG
		GACGAGGCCGACTACTACTGCCAGCAGTTCACC
		TCCTCTCCATTCACCTTTGGCACCGGCACCAAAG
		TGACAGTTCTT
Antibody B-H.1H LC-5		
SEQ ID NO: 20	LC CDR1 (Combined)	RASSSVNYIY
SEQ ID NO: 21	LC CDR2 (Combined))	YTSNLAP
SEQ ID NO: 22	LC CDR3 (Combined)	QQFTSSPFT
SEQ ID NO: 30	VL	SNELTQPPSVSVSPGQTARITCRASSSVNYIYWYQQ
		KSGQAPVLVIYYTSNLAPGIPERFSGSGSGNMYTLT
		ISGAQVEDEADYYCQQFTSSPFTFGTGTKVTVL
SEQ ID NO: 38	DNA VL	TCTAATGAGCTGACCCAGCCTCCTTCCGTGTCCG
		TGTCTCCTGGACAGACCGCCAGAATTACCTGCCG
		GGCCTCCTCCTCCGTGAACTACATCTACTGGTAT
		CAGCAGAAGTCCGGCCAGGCTCCTGTGCTCGTG
		ATCTACTACACCTCCAATCTGGCCCCTGGCATCC
		CTGAGAGATTCTCCGGATCTGGCTCCGGCAACAT
		GTACACCCTGACCATCTCTGGCGCCCAGGTGGA
		AGATGAGGCCGACTACTACTGCCAGCAGTTCAC
		CTCCTCTCCATTCACCTTTGGCACCGGCACCAAA
		GTGACAGTTCTT
Antibody B-H.1		
SEQ ID NO: 3280	Chain 1: Fc only	METDTLLLWVLLLWVPGSTGDKTHTCPPCPAPELL
		GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
		EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
		VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
		KGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFY
		PSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS
		KLTVDKSRWQQGNVFSCSVMHEALHNRFTQKSLS
		LSPGK
SEQ ID NO: 3281	Chain2: humanized B-H scFv	METDTLLLWVLLLWVPGSTGEVQLVESGGGLVQP
		GGSLRLSCAASGFTFSNFGMHWVRQAPGKGLEWV
		SYISSGSSTIYYADTLKGRFTISRDNSKNTLYLQMN
		SLRAEDTAVYYCARRGEGAMDYWGQGTTVTVSS
		GGGGSGGGGSGGGGSGGGGSDNQLTQSPSFLSAS
		VGDRVTITCRASSSVNYIYWYQQKPGKAPKLLIYY
		TSNLAPGVPSRFSGSGSGNEYTLTISSLQPEDFATY
		YCQQFTSSPFTFGQGTKLEIKGGGGSDKTHTCPPCP
		APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDV
		SHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
		RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK
		TISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAV
		KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF
		FLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
		QKSLSLSPGKGGGGSGGGGSGLNDIFEAQKIEWHE

TABLE 3

Constant region amino acid sequences of human IgG heavy chains and human kappa light chain

Human kappa constant region SEQ ID NO: 39	LC	RTVAAPSVFIFPPSDEQLKS GTASVVCLLN NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE KHKVYACEVT HQGLSSPVTK SFNRGEC
IgG4 (S228P) mutant constant region (EU Numbering) SEQ ID NO: 40	HC	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVD KRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQ EEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD GSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG
IgG1 wild type SEQ ID NO: 41	HC	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
IgG1 (N297A) mutant constant region (EU Numbering) SEQ ID NO: 42	HC	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GK
IgM constant delta CDC (P311A, P313S) SEQ ID NO: 73	HC	GSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNS DISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVVCKVQHPN GNKEKNVPLPVIAELPPKVSVFVPPRDGFFGNPRKSKLICQATGFSPR QIQVSWLREGKQVGSGVTTDQVQAEAKESGPTTYKVTSTLTIKESD WLGQSMFTCRVDHRGLTFQQNASSMCVPDQDTAIRVFAIPPSFASIF LTKSTKLTCLVTDLTTYDSVTISWTRQNGEAVKTHTNISESHPNATFS AVGEASICEDDWNSGERFTCTVTHTDLASSLKQTISRPKGVALHRPD VYLLPPAREQLNLRESATITCLVTGFSPADVFVQWMQRGQPLSPEKY VTSAPMPEPQAPGRYFAHSILTVSEEEWNTGETYTCVVAHEALPNRV TERTVDKSTGKPTLYNVSLVMSDTAGTCY
IgGA1 SEQ ID NO: 74	HC	ASPTSPKVFPLSLCSTQPDGNVVIACLVQGFFPQEPLSVTWSESGQGV TARNFPPSQDASGDLYTTSSQLTLPATQCLAGKSVTCHVKHYTNPSQ DVTVPCPVPSTPPTPSPSTPPTPSPSCCHPRLSLHRPALEDLLLGSEAN LTCTLTGLRDASGVTFTWTPSSGKSAVQGPPERDLCGCYSVSSVLPG CAEPWNHGKTFTCTAAYPESKTPLTATLSKSGNTFRPEVHLLPPPSEE LALNELVTLTCLARGFSPKDVLVRWLQGSQELPREKYLTWASRQEP SQGTTTFAVTSILRVAAEDWKKGDTFSCMVGHEALPLAFTQKTIDRL AGKPTHVNVSVVMAEVDGTCY
IgGA2 SEQ ID NO: 75	HC	ASPTSPKVFPLSLDSTPQDGNVVVACLVQGFFPQEPLSVTWSESGQN VTARNFPPSQDASGDLYTTSSQLTLPATQCPDGKSVTCHVKHYTNSS QDVTVPCRVPPPPPCCHPRLSLHRPALEDLLLGSEANLTCTLTGLRDA SGATFTWTPSSGKSAVQGPPERDLCGCYSVSSVLPGCAQPWNHGET FTCTAAHPELKTPLTANITKSGNTFRPEVHLLPPPSEELALNELVTLTC LARGFSPKDVLVRWLQGSQELPREKYLTWASRQEPSQGTTTYAVTSI LRVAAEDWKKGETFSCMVGHEALPLAFTQKTIDRMAGKPTHINVSV VMAEADGTCY
Human Ig_J chain SEQ ID NO: 76	HC	MKNHLLFWGVLAVFIKAVHVKAQEDERIVLVDNKCKCARITSRIIRS SEDPNEDIVERNIRIIVPLNNRENISDPTSPLRTRFVYHLSDLCKKCDPT EVELDNQIVTATQSNICDEDSATETCYTYDRNKCYTAVVPLVYGGET KMVETALTPDACYPD

Anti-TCRβV5 Antibodies

Accordingly, in one aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to human TCRβV5. In some embodiments, the TCRβV5 subfamily comprises TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01, or a variant thereof.

TABLE 10

Amino acid sequences for anti TCRβ V5 antibodies

Murine antibody C			
SEQ ID NO: 232	VH		DIQMTQTTSSLSASLGDRVTISCSASQGISNYLNWYQQKPDGTVKLLI YYTSSLHSGVPSRFSGSGSGTDYSLTISNLEPEDIATYYCQQYSKLPRT FGGGTKVEIK
SEQ ID NO: 233	VL		QVQLKESGPGLVAPSQSLSITCTVSGFSLTAYGVNWVRQPPGKGLE WLGMIWGDGNTDYNSALKSRLSISKDNSKSQVFLKMNSLQTDDTAR YYCARDRVTATLYAMDYWGQGTSVTVSS
Humanized antibody C (C-H antibody)			
Variable light chain (VL)			
SEQ ID NO: 3000	VL	C-H.1	DIQMTQSPSPLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTEYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3001	VL	C-H.2	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3002	VL	C-H.3	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKVVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED VATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3003	VL	C-H.4	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED VATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3004	VL	C-H.5	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTFTISSLQPED IATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3005	VL	C-H.6	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKTVKLLIYYTSSLHSGIPSRFSGSGSGTDYTLTIRSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3006	VL	C-H.7	AIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3007	VL	C-H.8	DIQMTQSPSSVSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3008	VL	C-H.9	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKRLIYYTSSLHSGVPSRFSGSGSGTEYTLTISNLQPE DFATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3009	VL	C-H.10	AIRMTQSPFSLSASVGDRVTITCSASQGISNYLNWYQQKP AKAVKLFIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3010	VL	C-H.11	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKRLIYYTSSLHSGVPSRFSGSGSGTEYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3011	VL	C-H.12	DIQMTQSPSTLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKLLIYYTSSLHSGVPSRFSGSGSGTEYTLTISSLQPDD FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO:3012	VL	C-H.13	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKSLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3013	VL	C-H.14	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKP GKAVKSLIYYTSSLHSGVPSKFSGSGSGTDYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3014	VL	C-H.15	DIQMTQSPSSLSASVGDRVTITCSASQGISNYLNWYQQKPE KAVKSLIYYTSSLHSGVPSRFSGSGSGTDYTLTISSLQPEDF ATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3015	VL	C-H.16	DIQMTQSPSAMSASVGDRVTITCSASQGISNYLNWYQQKP GKVVKRLIYYTSSLHSGVPSRFSGSGSGTEYTLTISSLQPED FATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3016	VL	C-H.17	DIVMTQSPDSLAVSLGERATINCSASQGISNYLNWYQQKP GQPVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLTISSLQAE DVAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3017	VL	C-H.18	EIVMTQSPGTLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPDRFSGSGSGTDYTLTISRLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3018	VL	C-H.19	EIVMTQSPPTLSLSPGERVTLSCSASQGISNYLNWYQQKPG QAVKLLIYYTSSLHSGIPARFSGSGSGTDYTLTISSLQPEDF AVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3019	VL	C-H.20	EIVMTQSPPTLSLSPGERVTLSCSASQGISNYLNWYQQKPG QAVKLLIYYTSSLHSSIPARFSGSGSGTDYTLTISSLQPEDF AVYYCQQYSKLPRTFGGGTKVEIK

TABLE 10-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3020	VL	C-H.21	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGSGTDYTLTISSLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3021	VL	C-H.22	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGSGTDYTLTISRLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3022	VL	C-H.23	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPDRFSGSGSGTDYTLTISRLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3023	VL	C-H.24	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GLAVKLLIYYTSSLHSGIPDRFSGSGSGTDYTLTISRLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3024	VL	C-H.25	DIQMIQSPSFLSASVGDRVSIICSASQGISNYLNWYLQKPG KSVKLFIYYTSSLHSGVSSRFSGRGSGTDYTLTIISLKPEDF AAYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3025	VL	C-H.26	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGSGTDYTLTISSLQPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3026	VL	C-H.27	EIVMTQSPATLSLSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGPGTDYTLTISSLEPED FAVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3027	VL	C-H.28	DIVMTQTPLSLSVTPGQPASISCSASQGISNYLNWYLQKPG QSVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3028	VL	C-H.29	DIVMTQTPLSLSVTPGQPASISCSASQGISNYLNWYLQKPG QPVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3029	VL	C-H.30	DIVMTQSPAFLSVTPGEKVTITCSASQGISNYLNWYQQKP DQAVKLLIYYTSSLHSGVPSRFSGSGSGTDYTFTISSLEAED AATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3030	VL	C-H.31	DIVMTQSPLSLPVTPGEPASISCSASQGISNYLNWYLQKPG QSVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3031	VL	C-H.32	DIVMTQTPLSLPVTPGEPASISCSASQGISNYLNWYLQKPG QSVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3032	VL	C-H.33	EIVMTQSPATLSVSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGSGTEYTLTISILQSEDF AVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3033	VL	C-H.34	EIVMTQSPATLSVSPGERATLSCSASQGISNYLNWYQQKP GQAVKLLIYYTSSLHSGIPARFSGSGSGTEYTLTISSLQSED F AVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3034	VL	C-H.35	DIVMTQSPLSLPVTLGQPASISCSASQGISNYLNWYQQRPG QSVKRLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3035	VL	C-H.36	EITMTQSPAFMSATPGDKVNISCSASQGISNYLNWYQQKP GEAVKFIIYYTSSLHSGIPPRFSGSGYGTDYTLTINNIESEDA AVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3036	VL	C-H.37	DIVMTQTPLSSPVTLGQPASISCSASQGISNYLNWYQQRPG QPVKLLIYYTSSLHSGVPDRFSGSGAGTDYTLKISRVEAED VGVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3037	VL	C-H.38	EIVMTQSPDFQSVTPKEKVTITCSASQGISNYLNWYQQKP DQSVKLLIYYTSSLHSGVPSRFSGSGSGTDYTLTINSLEAE D AATYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3038	VL	C-H.39	EIVMTQTPLSLSITPGEQASISCSASQGISNYLNWYLQKARP VVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAEDF GVYYCQQYSKLPRTFGGGTKVEIK
SEQ ID NO: 3039	VL	C-H.40	EIVMTQTPLSLSITPGEQASMSCSASQGISNYLNWYLQKAR PVVKLLIYYTSSLHSGVPDRFSGSGSGTDYTLKISRVEAED FGVYYCQQYSKLPRTFGGGTKVEIK
Variable HEAVY chain (VH)			
SEQ ID NO: 3040	VH	C-H.1	QVTLKESGPVLVKPTETLTLTCTVSGFSLTAYGVNWVRQP PGKALEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVV LTMTNMDPVDTATYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3041	VH	C-H.2	QVTLKESGPALVKPTETLTLTCTVSGFSLTAYGVNWVRQP PGKALEWLGMIWGDGNTDYNSALKSRLIISKDNSKSQVV LTMTNMDPVDTATYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3042	VH	C-H.3	QVTLKESGPALVKPTQTLTLTCTVSGFSLTAYGVNWVRQP PGKALEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVV LTMTNMDPVDTATYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3043	VH	C-H.4	QVQLQESGPGLVKPSGTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS

TABLE 10-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3044	VH	C-H.5	QVTLKESGPTLVKPTQTLTLTCTVSGFSLTAYGVNWVRQP PGKALEWLGMIWGDGNTDYNSALKSRLTITKDNSKSQVV LTMTNMDPVDTATYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3045	VH	C-H.6	QVTLKESGPALVKPTQTLTLTCTVSGFSLTAYGVNWVRQP PGKALEWLGMIWGDGNTDYNSALKSRLTITKDNSKSQVV LTMTNMDPVDTATYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3046	VH	C-H.7	QVQLQESGPGLVKPSQTLSLTCTVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3047	VH	C-H.8	QVQLQESGPGLVKPSETLSLTCTVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3048	VH	C-H.9	QVQLQESGPGLVKPSQTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3049	VH	C-H.10	QVQLQESGPGLVKPSDTLSLTCTVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3050	VH	C-H.11	QVQLQESGPGLVKPSQTLSLTCTVSGFSLTAYGVNWVRQ HPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3051	VH	C-H.12	QVQLQESGPGLVKPSQTLSLTCTVSGFSLTAYGVNWVRQP AGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3052	VH	C-H.13	QVQLQESGPGLVKPSQTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAVDTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3053	VH	C-H.14	QVQLQESGPGLVKPSETLSLTCTVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSHVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3054	VH	C-H.15	QVQLQESGPGLVKPSETLSLTCAVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3055	VH	C-H.16	QVQLQESGPGLVKPSQTLSLTCAVYGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3056	VH	C-H.17	RVQLQESGPGLVKPSETLSLTCTVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVP LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3057	VH	C-H.18	QVQLQESGPGLVKPSQTLSLTCTVSGFSLTAYGVNWVRQ HPGKGLEWLGMIWGDGNTDYNSALKSLLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3058	VH	C-H.19	QVQLQESGPGLVKPSDTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTALDTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3059	VH	C-H.20	QVQLQESGPGLVKPSDTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAVDTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3060	VH	C-H.21	QVQLQESGSGLVKPSQTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3061	VH	C-H.22	EVQLVESGGGLVQPGRSLRLSCTVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSIV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3062	VH	C-H.23	EVQLVESGGGLVQPGPSLRLSCTVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSIV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS

TABLE 10-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3063	VH	C-H.24	QVQLQESGSGLVKPSQTLSLTCAVSGFSLTAYGVNWVRQ SPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3064	VH	C-H.25	QVQLQESGPGLVKPSETLSLTCTVSGFSLTAYGVNWVRQP AGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQVS LKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLVT VSS
SEQ ID NO: 3065	VH	C-H.26	EVQLVESGGGLVKPGRSLRLSCTVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSIV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3066	VH	C-H.27	QVQLQESGPGLVKPSETLSLTCAVYGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV YLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3067	VH	C-H.28	QVQLQESGPGLVKPSDTLSLTCAVSGFSLTAYGVNWVRQ PPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQV SLKLSSVTAVDTGVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3068	VH	C-H.29	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSSV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3069	VH	C-H.30	EVQLVESGGGLVKPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3070	VH	C-H.31	QVQLQQSGPGLVKPSQTLSLTCAVSGFSLTAYGVNWVRQ SPSRGLEWLGMIWGDGNTDYNSALKSRLTINKDNSKSQV SLQLNSVTPEDTAVYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3071	VH	C-H.32	QVQLVESGGGLVQPGGSLRLSCSVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3072	VH	C-H.33	QVQLQQWGAGLLKPSETLSLTCAVYGFSLTAYGVNWVR QPPGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSQ VSLKLSSVTAADTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3073	VH	C-H.34	QVQLVESGGGVVQPGRSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSTSTV FLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3074	VH	C-H.35	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3075	VH	C-H.36	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSSV YLQMNSLRDEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3076	VH	C-H.37	EVQLLESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3077	VH	C-H.38	QVQLVESGGGLVKPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSSV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3078	VH	C-H.39	EVQLVESGGGLVQPGGSLKLSCAVSGFSLTAYGVNWVRQ ASGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLKTEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3079	VH	C-H.40	QVQLLESGGGLVKPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSSV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3080	VH	C-H.41	QVQLVESGGGVVQPGRSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3081	VH	C-H.42	QVQLVESGGGVVQPGRSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSRV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS

TABLE 10-continued

Amino acid sequences for anti TCRβ V5 antibodies			
SEQ ID NO: 3082	VH	C-H.43	QVQLVESGGGVVQPGRSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLAISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3083	VH	C-H.44	QVQLVESGGGVVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3084	VH	C-H.45	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3085	VH	C-H.46	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSSV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3086	VH	C-H.47	EVQLVESGGVVVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSSV YLQMNSLRTEDTALYYCARDRVTATLYAMDYWGQGTLV TVSS
SEQ ID NO: 3087	VH	C-H.48	EVQLVESGGGLVQPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKHNSKSTV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3088	VH	C-H.49	EVQLVESGGGLVKPGGSLRLSCAVSGFSLTAYGVNWVRQ APGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNAKSSV YLQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTL VTVSS
SEQ ID NO: 3089	VH	C-H.50	EVQLVESGGGLIQPGGSLRLSCAVSGFSLTAYGVNWVRQP PGKGLEWLGMIWGDGNTDYNSALKSRLTISKDNSKSTVY LQMNSLRAEDTAVYYCARDRVTATLYAMDYWGQGTLV TVSS

Antibody E comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 3284 and a light chain comprising the amino acid sequence of SEQ ID NO: 3285.

TABLE 11

Amino acid sequences for anti TCRβ V5 antibodies		
Murine antibody E		
SEQ ID NO: 3091	VH	QVQLQQSGPELVKPGASVKISCKASGYAFSSSWMNWVKQRPGQ GLEWIGRIYPGDGDTKYNGKFKGKATLTADKSSSTAYMHLSSLT SVDSAVYFCARRGTGGWYFDVWGAGTTVTVSS
SEQ ID NO: 3284	Heavy chain	METDTLLLWVLLLWVPGSTGQVQLQQSGPELVKPGASVKISCK ASGYAFSSSWMNWVKQRPGQGLEWIGRIYPGDGDTKYNGKFK GKATLTADKSSSTAYMHLSSLTSVDSAVYFCARRGTGGWYFDV WGAGTTVTVSSAKTTAPSVYPLAPVCGDTTGSSVTLGCLVKGYF SITCNVAHPASSTKVDKKIEPRGPTIKPCPPCKCPAPNLLGGPSVFI FPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQISWFVNNVEVHTA QTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPA PIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPE DIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNW VERNSYSCSVVHEGLHNHHTTKSFSRTPGK
SEQ ID NO: 3092	VL	DIVLTQSPASLAVSLGQRATISCRASESVDSSGNSFMHWYQQKP GQPPQLLIYRASNLESGIPARFSGSGSRTDFTLTINPVEADDVATF YCQQSFDDPFTFGSGTKLEIK
SEQ ID NO: 3285	Light chain	METDTLLLWVLLLWVPGSTGDIVLTQSPASLAVSLGQRATISCR ASESVDSSGNSFMHWYQQKPGQPPQLLIYRASNLESGIPARFSGS GSRTDFTLTINPVEADDVATFYCQQSFDDPFTFGSGTKLEIKRAD AAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSER QNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATH KTSTSPIVKSFNRNEC
Humanized antibody E (E-H antibody) Variable light chain (VL)		
SEQ ID NO: 3093	VL E-H.1	DIVLTQSPDSLAVSLGERATINCRASESVDSSGNSFMHWY QQKPGQPPQLLIYRASNLESGVPDRFSGSGSRTDFTLTISS LQAEDVAVYYCQQSFDDPFTFGQGTKLEIK

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3094	VL	E-H.2	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTDFTLTISS LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3095	VL	E-H.3	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTDFTLTISR LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3096	VL	E-H.4	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTDFTLTISS LQPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3097	VL	E-H.5	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDVATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3098	VL	E-H.6	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGPRTDFTLTISS LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3099	VL	E-H.7	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPDRFSGSGSRTDFTLTISR LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3100	VL	E-H.8	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKVPQLLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDVATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3101	VL	E-H.9	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKTPQLLIYRASNLESGIPSRFSGSGSRTDFTLTIRSL QPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3102	VL	E-H.10	EIVLTQSPGTLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPDRFSGSGSRTDFTLTISR LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3103	VL	E-H.11	EIVLTQSPATLSLSPGERATLSCRASESVDSSGNSFMHWY QQKPGLAPQLLIYRASNLESGIPDRFSGSGSRTDFTLTISR LEPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3104	VL	E-H.12	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3105	VL	E-H.13	DIQLTQSPSSVSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3106	VL	E-H.14	AIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3107	VL	E-H.15	DIQLTQSPSFLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTEFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3108	VL	E-H.16	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTDFTFTISS LQPEDIATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3109	VL	E-H.17	EIVLTQSPATLSVSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTEFTLTISIL QSEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3110	VL	E-H.18	EIVLTQSPATLSVSPGERATLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTEFTLTISSL QSEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3111	VL	E-H.19	AIRLTQSPFSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPAKAPQLFIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3112	VL	E-H.20	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQSLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3113	VL	E-H.21	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQRLIYRASNLESGVPSRFSGSGSRTEFTLTISN LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3114	VL	E-H.22	DIQLTQSPSTLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQLLIYRASNLESGVPSRFSGSGSRTEFTLTISS LQPDDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3115	VL	E-H.23	EIVLTQSPDFQSVTPKEKVTITCRASESVDSSGNSFMHWY QQKPDQSPQLLIYRASNLESGVPSRFSGSGSRTDFTLTINS LEAEDAATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3116	VL	E-H.24	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQSLIYRASNLESGVPSKFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3117	VL	E-H.25	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPGKAPQRLIYRASNLESGVPSRFSGSGSRTEFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3118	VL	E-H.26	DIVLTQTPLSLSVTPGQPASISCRASESVDSSGNSFMHWY LQKPGQPPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISR VEAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3119	VL	E-H.27	DIQLTQSPSSLSASVGDRVTITCRASESVDSSGNSFMHWY QQKPEKAPQSLIYRASNLESGVPSRFSGSGSRTDFTLTISS LQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3120	VL	E-H.28	EIVLTQSPPTLSLSPGERVTLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESGIPARFSGSGSRTDFTLTISS LQPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3121	VL	E-H.29	DIQLTQSPSAMSASVGDRVTITCRASESVDSSGNSFMHW YQQKPGKVPQRLIYRASNLESGVPSRFSGSGSRTEFTLTIS SLQPEDFATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO:3122	VL	E-H.30	DIVLTQSPLSLPVTPGEPASISCRASESVDSSGNSFMHWYL QKPGQSPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISRV EAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3123	VL	E-H.31	DIVLTQTPLSLPVTPGEPASISCRASESVDSSGNSFMHWYL QKPGQSPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISRV EAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3124	VL	E-H.32	DIVLTQTPLSLSVTPGQPASISCRASESVDSSGNSFMHWY LQKPGQSPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISR VEAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3125	VL	E-H.33	EIVLTQSPPTLSLSPGERVTLSCRASESVDSSGNSFMHWY QQKPGQAPQLLIYRASNLESSIPARFSGSGSRTDFTLTISSL QPEDFAVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3126	VL	E-H.34	DIVLTQSPLSLPVTLGQPASISCRASESVDSSGNSFMHWY QQRPGQSPQRLIYRASNLESGVPDRFSGSGSRTDFTLKISR VEAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3127	VL	E-H.35	DIVLTQTPLSSPVTLGQPASISCRASESVDSSGNSFMHWY QQRPGQPPQLLIYRASNLESGVPDRFSGSGARTDFTLKISR VEAEDVGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3128	VL	E-H.36	DIVLTQSPAFLSVTPGEKVTITCRASESVDSSGNSFMHWY QQKPDQAPQLLIYRASNLESGVPSRFSGSGSRTDFTFTISS LEAEDAATYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3129	VL	E-H.37	DIQLIQSPSFLSASVGDRVSIICRASESVDSSGNSFMHWYL QKPGKSPQLFIYRASNLESGVSSRFSGRGSRTDFTLTIISLK PEDFAAYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3130	VL	E-H.38	EIVLTQTPLSLSITPGEQASISCRASESVDSSGNSFMHWYL QKARPVPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISRV EAEDFGVYYCQQSFDDPFTFGQGTKLEIK
SEQ ID NO: 3131	VL	E-H.39	EIVLTQTPLSLSITPGEQASMSCRASESVDSSGNSFMHWY LQKARPVPQLLIYRASNLESGVPDRFSGSGSRTDFTLKISR VEAEDFGVYYCQQSFDDPFTFGQGTKLEIK

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3132	VL	E-H.40	EITLTQSPAFMSATPGDKVNISCRASESVDSSGNSFMHWY QQKPGEAPQFIIYRASNLESGIPPRFSGSGYRTDFTLTINNI ESEDAAYYYCQQSFDDPFTFGQGTKLEIK
			Variable HEAVY chain (VH)
SEQ ID NO: 3133	VH	E-H.1	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKS TSTAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3134	VH	E-H.2	QVQLVQSGAEVKKPGSSVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKS TSTAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3135	VH	E-H.3	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLTADKS TSTAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3136	VH	E-H.4	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQELEWIGRIYPGDGDTKYNGKFKGRATLTADKSI STAYMELSSLRSEDTATYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3137	VH	E-H.5	EVQLVQSGAEVKKPGATVKISCKASGYAFSSSWMNWVQ QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLTADKSTS TAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3138	VH	E-H.6	QVQLVQSGAEVKKTGSSVKVSCKASGYAFSSSWMNWV RQAPGQALEWIGRIYPGDGDTKYNGKFKGRATLTADKS MSTAYMELSSLRSEDTAMYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3139	VH	E-H.7	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQRLEWIGRIYPGDGDTKYNGKFKGRATLTADKS ASTAYMELSSLRSEDMAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3140	VH	E-H.8	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKS TSTAYMELRSLRSDDMAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3141	VH	E-H.9	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQRLEWIGRIYPGDGDTKYNGKFKGRATLTADKS ASTAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3142	VH	E-H.10	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKS TSTAYMELRSLRSDDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3143	VH	E-H.11	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKSI STAYMELSRLRSDDTAVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3144	VH	E-H.12	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGRATLTADKSI STAYMELSRLRSDDTVVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3145	VH	E-H.13	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQAPGQGLEWIGRIYPGDGDTKYNGKFKGWATLTADKS ISTAYMELSRLRSDDTAVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3146	VH	E-H.14	QVQLVQSGAEVKKPGASVKVSCKASGYAFSSSWMNWV RQATGQGLEWIGRIYPGDGDTKYNGKFKGRATLTANKSI STAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQGT TVTVSS

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3147	VH	E-H.15	QVQLVQSGSELKKPGASVKVSCKASGYAFSSSWMNWVR QAPGQGLEWIGRIYPGDGDTKYNGKFKGRAVLSADKSV STAYLQISSLKAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3148	VH	E-H.16	QVQLVQSGPEVKKPGTSVKVSCKASGYAFSSSWMNWVR QARGQRLEWIGRIYPGDGDTKYNGKFKGRATLTADKSTS TAYMELSSLRSEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3149	VH	E-H.17	EVQLVQSGAEVKKPGESLKISCKASGYAFSSSWMNWVR QMPGKGLEWIGRIYPGDGDTKYNGKFKGQATLSADKSIS TAYLQWSSLKASDTAMYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3150	VH	E-H.18	QVQLVQSGSELKKPGASVKVSCKASGYAFSSSWMNWVR QAPGQGLEWIGRIYPGDGDTKYNGKFKGRAVLSADKSV SMAYLQISSLKAEDTAVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3151	VH	E-H.19	QVQLVQSGHEVKQPGASVKVSCKASGYAFSSSWMNWV PQAPGQGLEWIGRIYPGDGDTKYNGKFKGRAVLSADKS ASTAYLQISSLKAEDMAMYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3152	VH	E-H.20	EVQLVQSGAEVKKPGESLKISCKASGYAFSSSWMNWVR QMPGKGLEWIGRIYPGDGDTKYNGKFKGQATLSADKPIS TAYLQWSSLKASDTAMYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3153	VH	E-H.21	EVQLVQSGAEVKKPGESLRISCKASGYAFSSSWMNWVR QMPGKGLEWIGRIYPGDGDTKYNGKFKGQATLSADKSIS TAYLQWSSLKASDTAMYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3154	VH	E-H.22	EVQLVQSGAEVKKPGESLRISCKASGYAFSSSWMNWVR QMPGKGLEWIGRIYPGDGDTKYNGKFKGHATLSADKSIS TAYLQWSSLKASDTAMYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3155	VH	E-H.23	QVQLVQSGAEVKKTGSSVKVSCKASGYAFSSSWMNWV RQAPRQALEWIGRIYPGDGDTKYNGKFKGRATLTADKS MSTAYMELSSLRSEDTAMYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3156	VH	E-H.24	EVQLVESGGGLVQPGRSLRLSCTASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS IAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3157	VH	E-H.25	EVQLVESGGGLVQPGPSLRLSCTASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS IAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3158	VH	E-H.26	QVQLQESGPGLVKPSQTLSLTCTASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3159	VH	E-H.27	QVQLQESGPGLVKPSGTLSLTCAASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3160	VH	E-H.28	EVQLVESGGGLVKPGRSLRLSCTASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS IAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3161	VH	E-H.29	EVQLVESGGGLVQPGGSLKLSCAASGYAFSSSWMNWVR QASGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3162	VH	E-H.30	QVQLQESGPGLVKPSQTLSLTCAASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3163	VH	E-H.31	EVQLVESGGGLVKPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3164	VH	E-H.32	EVQLVESGGALVKPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3165	VH	E-H.33	QVQLQESGPGLVKPSQTLSLTCAAYGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3166	VH	E-H.34	QVQLQESGSGLVKPSQTLSLTCAASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3167	VH	E-H.35	EVQLVESGGGLVQPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS SAYLQMNSLKTEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3168	VH	E-H.36	QVQLQESGPGLVKPSDTLSLTCTASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3169	VH	E-H.37	QVQLQESGPGLVKPSQTLSLTCTASGYAFSSSWMNWVR QHPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3170	VH	E-H.38	QVQLQESGPGLVKPSQTLSLTCTASGYAFSSSWMNWVR QHPGKGLEWIGRIYPGDGDTKYNGKFKGLATLSADKSKS QASLKLSSVTAADTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3171	VH	E-H.39	QVQLVESGGGVVQPGRSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMSSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3172	VH	E-H.40	QVQLVESGGGLVKPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKAK SSAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3173	VH	E-H.41	QVQLVESGGGLVQPGGSLRLSCSASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3174	VH	E-H.42	QVQLLESGGGLVKPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKAK SSAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQGT TVTVSS
SEQ ID NO: 3175	VH	E-H.43	EVQLVESGGGLVQPGGSLRLSCSASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMSSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3176	VH	E-H.44	QVQLQESGPGLVKPSDTLSLTCAASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAVDTAVYYCARRGTGGWYFDVWGQGTT VTVSS

TABLE 11-continued

Amino acid sequences for anti TCRβ V5 antibodies

SEQ ID NO: 3177	VH	E-H.45	QVQLQESGPGLVKPSQTLSLTCAASGYAFSSSWMNWVR QPPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS QASLKLSSVTAVDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3178	VH	E-H.46	EVQLVESGGGLVQPGGSLRLSCSASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYVQMSSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3179	VH	E-H.47	QVQLVDSGGGVVQPGRSLRLSCAASGYAFSSSWMNWV RQAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKS KSTAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQG TTVTVSS
SEQ ID NO: 3180	VH	E-H.48	QVQLVESGGGVVQPGRSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLRAEGTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3181	VH	E-H.49	QVQLVESGGGVVQPGRSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS
SEQ ID NO: 3182	VH	E-H.50	EVQLVESGGGLVQPGGSLRLSCAASGYAFSSSWMNWVR QAPGKGLEWIGRIYPGDGDTKYNGKFKGRATLSADKSKS TAYLQMNSLRAEDTAVYYCARRGTGGWYFDVWGQGTT VTVSS

In some embodiments, the anti-TCRβV5 antibody molecule comprises a VH and/or a VL of an antibody described in Table 10, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, the anti-TCRβV5 antibody molecule comprises a VH and a VL of an antibody described in Table 10, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, the anti-TCRβV5 antibody molecule comprises a VH and/or a VL of an antibody described in Table 11, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, the anti-TCRβV5 antibody molecule comprises a VH and a VL of an antibody described in Table 11, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

Anti-TCRβV10 Antibodies

Accordingly, in one aspect, the disclosure provides an anti-TCRβV antibody molecule that binds to a human TCRβV10 subfamily member. In some embodiments, TCRβV10 subfamily is also known as TCRβV12. In some embodiments, the TCRβV10 subfamily comprises: TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01, or a variant thereof.

TABLE 12

Amino acid sequences for anti TCRP V10 antibodies

Murine antibody D			
SEQ ID NO: 3183	VH		EVQLVESGGDLVKPGGSLKLSCAVSGFTFRSYGMSWVRQTPDKRL EWVALISSGGSYTYYTDSVKGRFTISRDNAKNTLYLQMSSLKSEDT AIYYCSRHGGNFFDYWGQGTTLTVSS
SEQ ID NO: 3184	VL		QIVLTQSPSIMSASPGEKVTMTCSVSSSVSYMHWYQQKSGTSPKR WIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWS SNPQYTFGGGTKLEIK
Humanized antibody D (D-H antibody) Variable light chain (VL)			
SEQ ID NO: 3185	VL	D-H.1	DIVLTQSPAFLSVTPGEKVTITCSVSSSVSYMHWYQQKPD QAPKLLIYDTSKLASGVPSRFSGSGSGTDYTFTISSLEAED AATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3186	VL	D-H.2	AIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3187	VL	D-H.3	DIQLTQSPSFLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTEYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

SEQ ID NO: 3188	VL	D-H.4	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3189	VL	D-H.5	DIQLTQSPSSVSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3190	VL	D-H.6	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KVPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED VATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3191	VL	D-H.7	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED VATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3192	VL	D-H.8	EIVLTQSPDFQSVTPKEKVTITCSVSSSVSYMHWYQQKPD QSPKLLIYDTSKLASGVPSRFSGSGSGTDYTLTINSLEAED AATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3193	VL	D-H.9	AIRLTQSPFSLSASVGDRVTITCSVSSSVSYMHWYQQKPA KAPKLFIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3194	VL	D-H.10	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDI ATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3195	VL	D-H.11	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTDYTLTISSLEPEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3196	VL	D-H.12	DIQLTQSPSTLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKLLIYDTSKLASGVPSRFSGSGSGTEYTLTISSLQPDD FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3197	VL	D-H.13	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KTPKLLIYDTSKLASGIPSRFSGSGSGTDYTLTIRSLQPEDF ATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3198	VL	D-H.14	EIVLTQSPPTLSLSPGERVTLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTDYTLTISSLQPED FAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3199	VL	D-H.15	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKRLIYDTSKLASGVPSRFSGSGSGTEYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3200	VL	D-H.16	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGPGTDYTLTISSLEPEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3201	VL	D-H.17	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTDYTLTISRLEPED FAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3202	VL	D-H.18	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTDYTLTISSLQPED FAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3203	VL	D-H.19	EIVLTQSPATLSVSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTEYTLTISSLQSEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3204	VL	D-H.20	EIVLTQSPATLSVSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPARFSGSGSGTEYTLTISILQSEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3205	VL	D-H.21	EIVLTQSPPTLSLSPGERVTLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASSIPARFSGSGSGTDYTLTISSLQPEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3206	VL	D-H.22	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKSLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

SEQ ID NO: 3207	VL	D-H.23	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKRLIYDTSKLASGVPSRFSGSGSGTEYTLTISNLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3208	VL	D-H.24	DIQLTQSPSAMSASVGDRVTITCSVSSSVSYMHWYQQKP GKVPKRLIYDTSKLASGVPSRFSGSGSGTEYTLTISSLQPE DFATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3209	VL	D-H.25	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPDRFSGSGSGTDYTLTISRLEPED FAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3210	VL	D-H.26	EIVLTQSPATLSLSPGERATLSCSVSSSVSYMHWYQQKPG LAPKLLIYDTSKLASGIPDRFSGSGSGTDYTLTISRLEPEDF AVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3211	VL	D-H.27	EIVLTQSPGTLSLSPGERATLSCSVSSSVSYMHWYQQKPG QAPKLLIYDTSKLASGIPDRFSGSGSGTDYTLTISRLEPED FAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3212	VL	D-H.28	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPG KAPKSLIYDTSKLASGVPSKFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3213	VL	D-H.29	DIQLTQSPSSLSASVGDRVTITCSVSSSVSYMHWYQQKPE KAPKSLIYDTSKLASGVPSRFSGSGSGTDYTLTISSLQPED FATYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3214	VL	D-H.30	DIVLTQSPDSLAVSLGERATINCSVSSSVSYMHWYQQKP GQPPKLLIYDTSKLASGVPDRFSGSGSGTDYTLTISSLQAE DVAVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3215	VL	D-H.31	EIVLTQTPLSLSITPGEQASMSCSVSSSVSYMHWYLQKAR PVPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DFGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3216	VL	D-H.32	EIVLTQTPLSLSITPGEQASISCSVSSSVSYMHWYLQKARP VPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAED FGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3217	VL	D-H.33	DIVLTQSPLSLPVTPGEPASISCSVSSSVSYMHWYLQKPG QSPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3218	VL	D-H.34	DIVLTQSPLSLPVTLGQPASISCSVSSSVSYMHWYQQRPG QSPKRLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3219	VL	D-H.35	DIVLTQTPLSLPVTPGEPASISCSVSSSVSYMHWYLQKPG QSPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3220	VL	D-H.36	DIVLTQTPLSLSVTPGQPASISCSVSSSVSYMHWYLQKPG QSPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3221	VL	D-H.37	DIVLTQTPLSLSVTPGQPASISCSVSSSVSYMHWYLQKPG QPPKLLIYDTSKLASGVPDRFSGSGSGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3222	VL	D-H.38	DIQLIQSPSFLSASVGDRVSIICSVSSSVSYMHWYLQKPGK SPKLFIYDTSKLASGVSSRFSGRGSGTDYTLTIISLKPEDFA AYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3223	VL	D-H.39	DIVLTQTPLSSPVTLGQPASISCSVSSSVSYMHWYQQRPG QPPKLLIYDTSKLASGVPDRFSGSGAGTDYTLKISRVEAE DVGVYYCQQWSSNPQYTFGQGTKLEIK
SEQ ID NO: 3224	VL	D-H.40	EITLTQSPAFMSATPGDKVNISCSVSSSVSYMHWYQQKP GEAPKFIIYDTSKLASGIPPRFSGSGYGTDYTLTINNIESED AAYYYCQQWSSNPQYTFGQGTKLEIK

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

			Variable HEAVY chain (VH)
SEQ ID NO: 3225	VH	D-H.1	EVQLVESGGGLVKPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3226	VH	D-H.2	EVQLVESGGALVKPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3227	VH	D-H.3	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3228	VH	D-H.4	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3229	VH	D-H.5	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN SLYLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3230	VH	D-H.6	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDMAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3231	VH	D-H.7	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGQFTISRDNAKN TLYLQMNSLRAEDMAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3232	VH	D-H.8	EVQLVESGGGLVKPGRSLRLSCTVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNIL YLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTVSS
SEQ ID NO: 3233	VH	D-H.9	EVQLVESGGGLVKPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3234	VH	D-H.10	EVQLVESGGGLVQPGGSLKLSCAVSGFTFRSYGMSWVR QASGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3235	VH	D-H.11	QVQLVESGGGVVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3236	VH	D-H.12	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMSSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3237	VH	D-H.13	EVQLVESGGGLVQPGGSLRLSCPVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNANNS LYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S
SEQ ID NO: 3238	VH	D-H.14	EVQLVESGGGLVQPGRSLRLSCTVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNIL YLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTVSS
SEQ ID NO: 3239	VH	D-H.15	EVQLVESGGGLVQPGPSLRLSCTVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNIL YLQMNSLKTEDTAVYYCSRHGGNFFDYWGQGTTVTVSS

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

SEQ ID NO: 3240	VH	D-H.16	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3241	VH	D-H.17	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRDEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3242	VH	D-H.18	QVQLVESGGGLVKPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3243	VH	D-H.19	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3244	VH	D-H.20	EVQLLESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S
SEQ ID NO: 3245	VH	D-H.21	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRHNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3246	VH	D-H.22	EVQLVESGGGLIQPGGSLRLSCAVSGFTFRSYGMSWVRQ PPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNTL YLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVSS
SEQ ID NO: 3247	VH	D-H.23	EVQLVESGGGLIQPGGSLRLSCAVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS s
SEQ ID NO: 3248	VH	D-H.24	EVQLVESGGGLVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTALYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3249	VH	D-H.25	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN RLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3250	VH	D-H.26	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEGTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3251	VH	D-H.27	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFAISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3252	VH	D-H.28	QVQLVDSGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3253	VH	D-H.29	EVQLVESGGGVVRPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTALYHCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3254	VH	D-H.30	EVQLVESGGVVVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN SLYLQMNSLRAEDTALYYCSRHGGNFFDYWGQGTTVTV SS

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

SEQ ID NO: 3255	VH	D-H.31	EVQLVESGGGVVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN SLYLQMNSLRTEDTALYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3256	VH	D-H.32	EVQLVESGGVVVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN SLYLQMNSLRTEDTALYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3257	VH	D-H.33	EVQLVETGGGLIQPGGSLRLSCAVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S
SEQ ID NO: 3258	VH	D-H.34	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QATGKGLEWVALISSGGSYTYYTDSVKGRFTISRENAKN SLYLQMNSLRAGDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3259	VH	D-H.35	EVQLVESRGVLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLHLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3260	VH	D-H.36	EVQLVESGGGLVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDMALYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3261	VH	D-H.37	QVQLVESGGGLVQPGGSLRLSCSVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3262	VH	D-H.38	EVQLVESGGGLVQPGGSLRLSCSVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYLQMSSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S
SEQ ID NO: 3263	VH	D-H.39	QVQLVESGGGVVQPGRSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSTN TLFLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3264	VH	D-H.40	QVQLLESGGGLVKPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNAKN SLYLQMNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3265	VH	D-H.41	EVQLVESGEGLVQPGGSLRLSCAVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYLQMGSLRAEDMAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3266	VH	D-H.42	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMGSLRAEDMAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3267	VH	D-H.43	EVQLVESGGGLVQPGGSLRLSCSVSGFTFRSYGMSWVRQ APGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKNT LYVQMSSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S
SEQ ID NO: 3268	VH	D-H.44	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFIISRDNSRNS LYLQKNRRRAEDMAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3269	VH	D-H.45	EVQLVESGGGLVQPGGSLRLSCAVSGFTFRSYGMSWVH QAPGKGLEWVALISSGGSYTYYTDSVKGRFIISRDNSRNT LYLQTNSLRAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S

TABLE 12-continued

Amino acid sequences for anti TCRP V10 antibodies

SEQ ID NO: 3270	VH	D-H.46	EVHLVESGGGLVQPGGALRLSCAVSGFTFRSYGMSWVR QATGKGLEWVALISSGGSYTYYTDSVKGRFTISRENAKN SLYLQMNSLRAGDTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3271	VH	D-H.47	EVQLVESGGGLVQPRGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNNLRAEGTAVYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3272	VH	D-H.48	EVQLVESGGGLVQPRGSLRLSCAVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTISRDNSKN TLYLQMNNLRAEGTAAYYCSRHGGNFFDYWGQGTTVT VSS
SEQ ID NO: 3273	VH	D-H.49	QVQLVQSGAEVKKPGASVKVSCKVSGFTFRSYGMSWVR QAPGKGLEWVALISSGGSYTYYTDSVKGRFTITRDNSTN TLYMELSSLRSEDTAVYYCSRHGGNFFDYWGQGTTVTV SS
SEQ ID NO: 3274	VH	D-H.50	QVQLVQSGSELKKPGASVKVSCKVSGFTFRSYGMSWVR QAPGQGLEWVALISSGGSYTYYTDSVKGRFVISRDNSVN TLYLQISSLKAEDTAVYYCSRHGGNFFDYWGQGTTVTVS S

In some embodiments, the anti-TCRβV10 antibody molecule comprises a VH or a VL of an antibody described in Table 12, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

In some embodiments, the anti-TCRβV10 antibody molecule comprises a VH and a VL of an antibody described in Table 12, or a sequence with at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or more identity thereto.

Antibody Molecules

In one embodiment, the antibody molecule binds to a cancer antigen, e.g., a tumor antigen or a stromal antigen. In some embodiments, the cancer antigen is, e.g., a mammalian, e.g., a human, cancer antigen. In other embodiments, the antibody molecule binds to an immune cell antigen, e.g., a mammalian, e.g., a human, immune cell antigen. For example, the antibody molecule binds specifically to an epitope, e.g., linear or conformational epitope, on the cancer antigen or the immune cell antigen.

In an embodiment, an antibody molecule is a monospecific antibody molecule and binds a single epitope. E.g., a monospecific antibody molecule having a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope.

In an embodiment an antibody molecule is a multispecific or multifunctional antibody molecule, e.g., it comprises a plurality of immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein). In an embodiment a multispecific antibody molecule comprises a third, fourth or fifth immunoglobulin variable domain. In an embodiment, a multispecific antibody molecule is a bispecific antibody molecule, a trispecific antibody molecule, or a tetraspecific antibody molecule.

In an embodiment a multispecific antibody molecule is a bispecific antibody molecule. A bispecific antibody has specificity for no more than two antigens. A bispecific antibody molecule is characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In an embodiment the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In an embodiment the first and second epitopes overlap. In an embodiment the first and second epitopes do not overlap. In an embodiment the first and second epitopes are on different antigens, e.g., the different proteins (or different subunits of a multimeric protein). In an embodiment a bispecific antibody molecule comprises a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a half antibody, or fragment thereof, having binding specificity for a first epitope and a half antibody, or fragment thereof, having binding specificity for a second epitope. In an embodiment a bispecific antibody molecule comprises a scFv or a Fab, or fragment thereof, have binding specificity for a first epitope and a scFv or a Fab, or fragment thereof, have binding specificity for a second epitope.

In an embodiment, an antibody molecule comprises a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (e.g., Fab, $F(ab')_2$, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In an embodiment an antibody molecule comprises or consists of a heavy chain and a light chain

(referred to herein as a half antibody. In another example, an antibody molecule includes two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')2, Fc, Fd, Fd, Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (e.g., humanized) antibodies, which may be produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies. These functional antibody fragments retain the ability to selectively bind with their respective antigen or receptor. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (e.g., IgG1, IgG2, IgG3, and IgG4) of antibodies. The a preparation of antibody molecules can be monoclonal or polyclonal. An antibody molecule can also be a human, humanized, CDR-grafted, or in vitro generated antibody. The antibody can have a heavy chain constant region chosen from, e.g., IgG1, IgG2, IgG3, or IgG4. The antibody can also have a light chain chosen from, e.g., kappa or lambda. The term "immunoglobulin" (Ig) is used interchangeably with the term "antibody" herein.

Examples of antigen-binding fragments of an antibody molecule include: (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a diabody (dAb) fragment, which consists of a VH domain; (vi) a camelid or camelized variable domain; (vii) a single chain Fv (scFv), see e.g., Bird et al. (1988) *Science* 242:423-426; and Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883); (viii) a single domain antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

Antibody molecules include intact molecules as well as functional fragments thereof. Constant regions of the antibody molecules can be altered, e.g., mutated, to modify the properties of the antibody (e.g., to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function).

Antibody molecules can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Examples include, but are not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. According to another aspect of the invention, a single domain antibody is a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 9404678, for example. For clarity reasons, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody to distinguish it from the conventional VH of four chain immunoglobulins. Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain; such VHHs are within the scope of the invention.

The VH and VL regions can be subdivided into regions of hypervariability, termed "complementarity determining regions" (CDR), interspersed with regions that are more conserved, termed "framework regions" (FR or FW).

The extent of the framework region and CDRs has been precisely defined by a number of methods (see, Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. et al. (1987) *J Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular's AbM antibody modeling software. See, generally, e.g., *Protein Sequence and Structure Analysis of Antibody Variable Domains*. In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg).

The terms "complementarity determining region," and "CDR," as used herein refer to the sequences of amino acids within antibody variable regions which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (HCDR1, HCDR2, HCDR3) and three CDRs in each light chain variable region (LCDR1, LCDR2, LCDR3).

The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) *JMB* 273, 927-948 ("Chothia" numbering scheme). As used herein, the CDRs defined according the "Chothia" number scheme are also sometimes referred to as "hypervariable loops."

For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia, the CDR amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3).

Each VH and VL typically includes three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

The antibody molecule can be a polyclonal or a monoclonal antibody.

The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. A monoclonal antibody can be made by hybridoma technology or by methods that do not use hybridoma technology (e.g., recombinant methods).

The antibody can be recombinantly produced, e.g., produced by phage display or by combinatorial methods, or by yeast display.

Phage display and combinatorial methods for generating antibodies are known in the art (as described in, e.g., Ladner et al. U.S. Pat. No. 5,223,409; Kang et al. International

Publication No. WO 92/18619; Dower et al. International Publication No. WO 91/17271; Winter et al. International Publication WO 92/20791; Markland et al. International Publication No. WO 92/15679; Breitling et al. International Publication WO 93/01288; McCafferty et al. International Publication No. WO 92/01047; Garrard et al. International Publication No. WO 92/09690; Ladner et al. International Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum Antibod Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffths et al. (1993) *EMBO J* 12:725-734; Hawkins et al. (1992) *J Mol Biol* 226:889-896; Clackson et al. (1991) *Nature* 352:624-628; Gram et al. (1992) *PNAS* 89:3576-3580; Garrad et al. (1991) *Bio/Technology* 9:1373-1377; Hoogenboom et al. (1991) *Nuc Acid Res* 19:4133-4137; and Barbas et al. (1991) *PNAS* 88:7978-7982, the contents of all of which are incorporated by reference herein).

The yeast display method for generating or identifying antibodies is known in the art, e.g., as described in Chao et al. (2006) *Nature Protocols* 1(2):755-68, the entire contents of which is incorporated by reference herein.

In one embodiment, the antibody is a fully human antibody (e.g., an antibody made in a mouse which has been genetically engineered to produce an antibody from a human immunoglobulin sequence), or a non-human antibody, e.g., a rodent (mouse or rat), goat, primate (e.g., monkey), camel antibody. Preferably, the non-human antibody is a rodent (mouse or rat antibody). Methods of producing rodent antibodies are known in the art.

Human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest are used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (see, e.g., Wood et al. International Application WO 91/00906, Kucherlapati et al. PCT publication WO 91/10741; Lonberg et al. International Application WO 92/03918; Kay et al. International Application 92/03917; Lonberg, N. et al. 1994 *Nature* 368:856-859; Green, L. L. et al. 1994 *Nature Genet.* 7:13-21; Morrison, S. L. et al. 1994 *Proc. Natl. Acad. Sci. USA* 81:6851-6855; Bruggeman et al. 1993 *Year Immunol* 7:33-40; Tuaillon et al. 1993 *PNAS* 90:3720-3724; Bruggeman et al. 1991 *Eur J Immunol* 21:1323-1326).

An antibody molecule can be one in which the variable region, or a portion thereof, e.g., the CDRs, are generated in a non-human organism, e.g., a rat or mouse. Chimeric, CDR-grafted, and humanized antibodies are within the invention. Antibody molecules generated in a non-human organism, e.g., a rat or mouse, and then modified, e.g., in the variable framework or constant region, to decrease antigenicity in a human are within the invention.

An "effectively human" protein is a protein that does substantially not evoke a neutralizing antibody response, e.g., the human anti-murine antibody (HAMA) response. HAMA can be problematic in a number of circumstances, e.g., if the antibody molecule is administered repeatedly, e.g., in treatment of a chronic or recurrent disease condition. A HAMA response can make repeated antibody administration potentially ineffective because of an increased antibody clearance from the serum (see, e.g., Saleh et al., *Cancer Immunol. Immunother.,* 32:180-190 (1990)) and also because of potential allergic reactions (see, e.g., LoBuglio et al., *Hybridoma,* 5:5117-5123 (1986)).

Chimeric antibodies can be produced by recombinant DNA techniques known in the art (see Robinson et al., International Patent Publication PCT/US86/02269; Akira, et al., European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al., European Patent Application 173,494; Neuberger et al., International Application WO 86/01533; Cabilly et al. U.S. Pat. No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better et al. (1988 *Science* 240:1041-1043); Liu et al. (1987) *PNAS* 84:3439-3443; Liu et al., 1987, *J. Immunol.* 139:3521-3526; Sun et al. (1987) PNAS 84:214-218; Nishimura et al., 1987, *Canc. Res.* 47:999-1005; Wood et al. (1985) *Nature* 314:446-449; and Shaw et al., 1988, *J. Natl Cancer Inst.* 80:1553-1559).

A humanized or CDR-grafted antibody will have at least one or two but generally all three recipient CDRs (of heavy and or light immuoglobulin chains) replaced with a donor CDR. The antibody may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. It is only necessary to replace the number of CDRs required for binding to the antigen. Preferably, the donor will be a rodent antibody, e.g., a rat or mouse antibody, and the recipient will be a human framework or a human consensus framework. Typically, the immunoglobulin providing the CDRs is called the "donor" and the immunoglobulin providing the framework is called the "acceptor." In one embodiment, the donor immunoglobulin is a non-human (e.g., rodent). The acceptor framework is a naturally-occurring (e.g., a human) framework or a consensus framework, or a sequence about 85% or higher, preferably 90%, 95%, 99% or higher identical thereto.

As used herein, the term "consensus sequence" refers to the sequence formed from the most frequently occurring amino acids (or nucleotides) in a family of related sequences (See e.g., Winnaker, From Genes to Clones (Verlagsgesellschaft, Weinheim, Germany 1987). In a family of proteins, each position in the consensus sequence is occupied by the amino acid occurring most frequently at that position in the family. If two amino acids occur equally frequently, either can be included in the consensus sequence. A "consensus framework" refers to the framework region in the consensus immunoglobulin sequence.

An antibody molecule can be humanized by methods known in the art (see e.g., Morrison, S. L., 1985, *Science* 229:1202-1207, by Oi et al., 1986, *BioTechniques* 4:214, and by Queen et al. U.S. Pat. Nos. 5,585,089, 5,693,761 and 5,693,762, the contents of all of which are hereby incorporated by reference).

Humanized or CDR-grafted antibody molecules can be produced by CDR-grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. See e.g., U.S. Pat. No. 5,225,539; Jones et al. 1986 *Nature* 321:552-525; Verhoeyan et al. 1988 *Science* 239:1534; Beidler et al. 1988 *J. Immunol.* 141:4053-4060; Winter U.S. Pat. No. 5,225,539, the contents of all of which are hereby expressly incorporated by reference. Winter describes a CDR-grafting method which may be used to prepare the humanized antibodies of the present invention (UK Patent Application GB 2188638A, filed on Mar. 26, 1987; Winter U.S. Pat. No. 5,225,539), the contents of which is expressly incorporated by reference.

Also within the scope of the invention are humanized antibody molecules in which specific amino acids have been substituted, deleted or added. Criteria for selecting amino acids from the donor are described in U.S. Pat. No. 5,585,089, e.g., columns 12-16 of U.S. Pat. No. 5,585,089, e.g., columns 12-16 of U.S. Pat. No. 5,585,089, the contents of which are hereby incorporated by reference. Other techniques for humanizing antibodies are described in Padlan et al. EP 519596 A1, published on Dec. 23, 1992.

The antibody molecule can be a single chain antibody. A single-chain antibody (scFV) may be engineered (see, for example, Colcher, D. et al. (1999) *Ann NY Acad Sci* 880: 263-80; and Reiter, Y. (1996) *Clin Cancer Res* 2:245-52). The single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein.

In yet other embodiments, the antibody molecule has a heavy chain constant region chosen from, e.g., the heavy chain constant regions of IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE; particularly, chosen from, e.g., the (e.g., human) heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4. In another embodiment, the antibody molecule has a light chain constant region chosen from, e.g., the (e.g., human) light chain constant regions of kappa or lambda. The constant region can be altered, e.g., mutated, to modify the properties of the antibody (e.g., to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, and/or complement function). In one embodiment the antibody has: effector function; and can fix complement. In other embodiments the antibody does not; recruit effector cells; or fix complement. In another embodiment, the antibody has reduced or no ability to bind an Fc receptor. For example, it is a isotype or subtype, fragment or other mutant, which does not support binding to an Fc receptor, e.g., it has a mutagenized or deleted Fc receptor binding region.

Methods for altering an antibody constant region are known in the art. Antibodies with altered function, e.g. altered affinity for an effector ligand, such as FcR on a cell, or the Cl component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see e.g., EP 388,151 A1, U.S. Pat. Nos. 5,624,821 and 5,648,260, the contents of all of which are hereby incorporated by reference). Similar type of alterations could be described which if applied to the murine, or other species immunoglobulin would reduce or eliminate these functions.

An antibody molecule can be derivatized or linked to another functional molecule (e.g., another peptide or protein). As used herein, a "derivatized" antibody molecule is one that has been modified. Methods of derivatization include but are not limited to the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin. Accordingly, the antibody molecules of the invention are intended to include derivatized and otherwise modified forms of the antibodies described herein, including immunoadhesion molecules. For example, an antibody molecule can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody molecule is produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (e.g., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Multispecific or Multifunctional Antibody Molecules

Exemplary structures of multispecific and multifunctional molecules defined herein are described throughout. Exemplary structures are further described in: Weidle U et al. (2013) The Intriguing Options of Multispecific Antibody Formats for Treatment of Cancer. *Cancer Genomics & Proteomics* 10: 1-18 (2013); and Spiess C et al. (2015) Alternative molecular formats and therapeutic applications for bispecific antibodies. *Molecular Immunology* 67: 95-106; the full contents of each of which is incorporated by reference herein).

In embodiments, multispecific antibody molecules can comprise more than one antigen-binding site, where different sites are specific for different antigens. In embodiments, multispecific antibody molecules can bind more than one (e.g., two or more) epitopes on the same antigen. In embodiments, multispecific antibody molecules comprise an antigen-binding site specific for a target cell (e.g., cancer cell) and a different antigen-binding site specific for an immune effector cell. In one embodiment, the multispecific antibody molecule is a bispecific antibody molecule. Bispecific antibody molecules can be classified into five different structural groups: (i) bispecific immunoglobulin G (BsIgG); (ii) IgG appended with an additional antigen-binding moiety; (iii) bispecific antibody fragments; (iv) bispecific fusion proteins; and (v) bispecific antibody conjugates.

BsIgG is a format that is monovalent for each antigen. Exemplary BsIgG formats include but are not limited to crossMab, DAF (two-in-one), DAF (four-in-one), DutaMab, DT-IgG, knobs-in-holes common LC, knobs-in-holes assembly, charge pair, Fab-arm exchange, SEEDbody, triomab, LUZ-Y, Fcab, κλ-body, orthogonal Fab. See Spiess et al. Mol. Immunol. 67(2015):95-106. Exemplary BsIgGs include catumaxomab (Fresenius Biotech, Trion Pharma, Neopharm), which contains an anti-CD3 arm and an anti-EpCAM arm; and ertumaxomab (Neovii Biotech, Fresenius Biotech), which targets CD3 and HER2. In some embodiments, BsIgG comprises heavy chains that are engineered for heterodimerization. For example, heavy chains can be engineered for heterodimerization using a "knobs-into-holes" strategy, a SEED platform, a common heavy chain (e.g., in κλ-bodies), and use of heterodimeric Fc regions. See Spiess et al. Mol. Immunol. 67(2015):95-106. Strategies that have been used to avoid heavy chain pairing of homodimers in BsIgG include knobs-in-holes, duobody, azymetric, charge pair, HA-TF, SEEDbody, and differential protein A affinity. See Id. BsIgG can be produced by separate expression of the component antibodies in different host cells and subsequent purification/assembly into a BsIgG. BsIgG can also be produced by expression of the component antibodies in a single host cell. BsIgG can be purified using affinity chromatography, e.g., using protein A and sequential pH elution.

IgG appended with an additional antigen-binding moiety is another format of bispecific antibody molecules. For example, monospecific IgG can be engineered to have bispecificity by appending an additional antigen-binding unit onto the monospecific IgG, e.g., at the N- or C-terminus of either the heavy or light chain. Exemplary additional antigen-binding units include single domain antibodies (e.g., variable heavy chain or variable light chain), engineered protein scaffolds, and paired antibody variable domains (e.g., single chain variable fragments or variable fragments). See Id. Examples of appended IgG formats include dual variable domain IgG (DVD-Ig), IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)—IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig, zybody, and DVI-IgG (four-in-one). See

Spiess et al. Mol. Immunol. 67(2015):95-106. An example of an IgG-scFv is MM-141 (Merrimack Pharmaceuticals), which binds IGF-1R and HER3. Examples of DVD-Ig include ABT-981 (AbbVie), which binds IL-1α and IL-1β; and ABT-122 (AbbVie), which binds TNF and IL-17A.

Bispecific antibody fragments (BsAb) are a format of bispecific antibody molecules that lack some or all of the antibody constant domains. For example, some BsAb lack an Fc region. In embodiments, bispecific antibody fragments include heavy and light chain regions that are connected by a peptide linker that permits efficient expression of the BsAb in a single host cell. Exemplary bispecific antibody fragments include but are not limited to nanobody, nanobody-HAS, BiTE, Diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, triple body, miniantibody, minibody, TriBi minibody, scFv-CH3 KIH, Fab-scFv, scFv-CH-CL-scFv, F(ab')2, F(ab')2-scFv2, scFv-KIH, Fab-scFv-Fc, tetravalent HCAb, scDiabody-Fc, Diabody-Fc, tandem scFv-Fc, and intrabody. See Id. For example, the BiTE format comprises tandem scFvs, where the component scFvs bind to CD3 on T cells and a surface antigen on cancer cells

Bispecific fusion proteins include antibody fragments linked to other proteins, e.g., to add additional specificity and/or functionality. An example of a bispecific fusion protein is an immTAC, which comprises an anti-CD3 scFv linked to an affinity-matured T-cell receptor that recognizes HLA-presented peptides. In embodiments, the dock-and-lock (DNL) method can be used to generate bispecific antibody molecules with higher valency. Also, fusions to albumin binding proteins or human serum albumin can be extend the serum half-life of antibody fragments. See Id.

In embodiments, chemical conjugation, e.g., chemical conjugation of antibodies and/or antibody fragments, can be used to create BsAb molecules. See Id. An exemplary bispecific antibody conjugate includes the CovX-body format, in which a low molecular weight drug is conjugated site-specifically to a single reactive lysine in each Fab arm or an antibody or fragment thereof. In embodiments, the conjugation improves the serum half-life of the low molecular weight drug. An exemplary CovX-body is CVX-241 (NCT01004822), which comprises an antibody conjugated to two short peptides inhibiting either VEGF or Ang2. See Id.

The antibody molecules can be produced by recombinant expression, e.g., of at least one or more component, in a host system. Exemplary host systems include eukaryotic cells (e.g., mammalian cells, e.g., CHO cells, or insect cells, e.g., SF9 or S2 cells) and prokaryotic cells (e.g., *E. coli*). Bispecific antibody molecules can be produced by separate expression of the components in different host cells and subsequent purification/assembly. Alternatively, the antibody molecules can be produced by expression of the components in a single host cell. Purification of bispecific antibody molecules can be performed by various methods such as affinity chromatography, e.g., using protein A and sequential pH elution. In other embodiments, affinity tags can be used for purification, e.g., histidine-containing tag, myc tag, or streptavidin tag.

Exemplary Bispecific Molecules

In an aspect, a multispecific molecule disclosed herein comprises a sequence disclosed herein, e.g., a sequence chosen from SEQ ID NOs: 1004-1007, 3275-3277, 3286, or 3287, or a sequence with at least 85%, 90%, 955, 96%, 97%, 98%, 99% or more identity thereto. In some embodiments, a multispecific molecule disclosed herein comprises a leader sequence comprising the amino acid sequence of SEQ ID NO: 3288. In some embodiments, a multispecific molecule disclosed herein does not comprise a leader sequence comprising the amino acid sequence of SEQ ID NO: 3288.

Molecule F: aCD19 x aVb6.5

Molecule F comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1004 and a light chain comprising the amino acid sequence of SEQ ID NO: 1005.

Molecule F.1
(heavy chain) (Tcrvbeta6_5 scFv/anti-CD19 heavy chain)
SEQ ID NO: 1004

METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVR

QAPGQGLEWMGWFFPGSGNIKYNEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYC

AGSYYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSFLSASV

GDRVTITCKASQNVGINVVWHQQKPGKAPKALIYSSSHRYSGVPSRFSGSGSGTEFTLTI

SSLQPEDFATYFCQQFKSYPLTFGQGTKLEIKGGGGSQVTLRESGPALVKPTQTLTLTCT

FSGFSLSTSGMGVGWIRQPPGKALEWLAHIWWDDDKRYNPALKSRLTISKDTSKNQVF

LTMTNMDPVDTATYYCARMELWSYYFDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTS

GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT

QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR

TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD

WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG

FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE

ALHNHYTQKSLSLSPGK

-continued

Molecule F.2
(light chain) (anti-CD19 light chain)

SEQ ID NO: 1005

METPAQLLFLLLLWLPDTTGENVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKP

GQAPRLLIYDTSKLASGIPARFSGSGSGTDHTLTISSLEPEDFAVYYCFQGSVYPFTFGQG

TKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ

ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

In an aspect, a multispecific molecule disclosed herein comprises SEQ ID NO: 1004 and/or SEQ ID NO: 1005 or a sequence with at least 85%, 90%, 955, 96%, 97%, 98%, 99% or more identity thereto.

Molecule G: aBCMA x aVb6.5

Molecule G comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 1006 and a light chain comprising the amino acid sequence of SEQ ID NO: 1007.

Molecule G.1
(heavy chain)

SEQ ID NO: 1006

METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVR

QAPGQGLEWMGWFFPGSGNIKYNEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYC

AGSYYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSFLSASV

GDRVTITCKASQNVGINVVWHQQKPGKAPKALIYSSSHRYSGVPSRFSGSGSGTEFTLTI

SSLQPEDFATYFCQQFKSYPLTFGQGTKLEIKGGGGSQVQLVESGGGVVQPGRSLRLSC

AASGIDFSRYWMSWVRQAPGKGLEWVGEINPDSSTINYAPSLKDRFTISRDNSKNTLYL

QMSSLRAEDTAVYYCASLYYDYGDAMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTS

GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT

QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR

TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQD

WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKG

FYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE

ALHNRFTQKSLSLSPGK

Molecule G2
(light chain)

SEQ ID NO: 1007

METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCKASQSVDSNVAWYQQ

KPEKAPKALIFSASLRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQYNNYPLTFG

QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN

SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

In an aspect, a multispecific molecule disclosed herein comprises SEQ ID NO: 1006 and/or SEQ ID NO: 1007 or a sequence with at least 85%, 90%, 955, 96%, 97%, 98%, 99% or more identity thereto.

Molecule H: aBCMA x aTCRvbeta6_5

Molecule H comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 3275, a light chain comprising the amino acid sequence of SEQ ID NO: 3277, and a second heavy chain comprising the amino acid sequence of SEQ ID NO: 3276.

Molecule H.1
(anti-BCMA heavy chain)

SEQ ID NO: 3275

METDTLLLWVLLLWVPGSTGQVQLVESGGGVVQPGRSLRLSCAASGIDFSRYWMSWV

RQAPGKGLEWVGEINPDSSTINYAPSLKDRFTISRDNSKNTLYLQMSSLRAEDTAVYYC

ASLYYDYGDAMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV

DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP

EVKFNWYVDGVEVHNAKTKPREEQYNATYRVVSVLTVLHQDWLNGKEYKCKVSNKA

LPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQP

ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP

GK

Molecule H.2
(TCRvbeta_6_5 scFv humanized)

SEQ ID NO: 3276

METDTLLLWVLLLWVPGSTGQVQLVQSGAEVKKPGSSVKVSCKASGYSFTTYYIHWVR

QAPGQGLEWMGWFFPGSGNIKYNEKFKGRVTITADTSTSTAYMELSSLRSEDTAVYYC

AGSYYSYDVLDYWGQGTTVTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQSPSFLSASV

GDRVTITCKASQNVGINVVWHQQKPGKAPKALIYSSSHRYSGVPSRFSGSGSGTEFTLTI

SSLQPEDFATYFCQQFKSYPLTFGQGTKLEIKGGGGSGGGGSDKTHTCPPCPAPELLGGP

SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQY

ASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSR

EEMTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDK

SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Molecule H.3
(anti-BCMA light chain)

SEQ ID NO: 3277

METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCKASQSVDSNVAWYQQ

KPEKAPKALIFSASLRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQYNNYPLTFG

QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN

SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

In an aspect, a multispecific molecule disclosed herein comprises SEQ ID NO: 3275, SEQ ID NO: 3276, and/or SEQ ID NO: 3277 or a sequence with at least 85%, 90%, 955, 96%, 97%, 98%, 99% or more identity thereto.

Molecule I: Half Arm BCMA Fab with c-Terminal scFv TCRvbeta

Molecule I comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 3286, a light chain comprising the amino acid sequence of SEQ ID NO: 3277, and a second heavy chain comprising the amino acid sequence of SEQ ID NO: 3287.

Molecule 1.1
(heavy chain 1)
SEQ ID NO: 3286

METDTLLLWVLLLWVPGSTGQVQLVESGGGVVQPGRSLRLSCAASGIDFSRYWMSWV

RQAPGKGLEWVGEINPDSSTINYAPSLKDRFTISRDNSKNTLYLQMSSLRAEDTAVYYC

ASLYYDYGDAMDYWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV

DKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP

EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA

LPAPIEKTISKAKGQPREPQVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQP

ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP

GKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQA

PGKGLEWVSRIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLKTEDTAVYYC

VRHGNFGNSYVSWFAYWGQGTLVTVSSGGGGSGGGGSGGGGSGGGGSQAVVTQEPSL

TVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPWTPARFSGSLL

GGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLTVL

Molecule 1.2
(light chain)
SEQ ID NO: 3277

METDTLLLWVLLLWVPGSTGDIQMTQSPSSLSASVGDRVTITCKASQSVDSNVAWYQQ

KPEKAPKALIFSASLRFSGVPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQYNNYPLTFG

QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN

SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Molecule 1.3
(heavy chain 2)
SEQ ID NO: 3287

METDTLLLWVLLLWVPGSTGDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT

CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG

KEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLSCAVKGFYPSD

IAVEWESNGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHN

HYTQKSLSLSPGK

In an aspect, a multispecific molecule disclosed herein comprises SEQ ID NO: 3286, SEQ ID NO: 3277, and/or SEQ ID NO: 3287 or a sequence with at least 85%, 90%, 955, 96%, 97%, 98%, 99% or more identity thereto.

Antibody-Like Frameworks or Scaffolds

A wide variety of antibody/immunoglobulin frameworks or scaffolds can be employed in the anti-TCRvb antibody molecules disclosed herein or multifunctional formats thereof so long as the resulting polypeptide includes at least one binding region which specifically binds to the target antigen, e.g., a TCRvb, a tumor antigen, among others. Such frameworks or scaffolds include the 5 main idiotypes of human immunoglobulins, or fragments thereof, and include immunoglobulins of other animal species, preferably having humanized aspects. Novel frameworks, scaffolds and fragments continue to be discovered and developed by those skilled in the art.

In one embodiment, the anti-TCRvb antibody molecules disclosed herein or multifunctional formats thereof include non-immunoglobulin based antibodies using non-immunoglobulin scaffolds onto which CDRs can be grafted. Any non-immunoglobulin frameworks and scaffolds may be employed, as long as they comprise a binding region specific for the target antigen (e.g., TCRvb or a tumor antigen).

Exemplary non-immunoglobulin frameworks or scaffolds include, but are not limited to, fibronectin (Compound Therapeutics, Inc., Waltham, MA), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, MA, and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immuno-pharmaceuticals (Trubion Pharmaceuticals Inc., Seattle, WA), maxybodies (Avidia, Inc., Mountain View, CA), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

Fibronectin scaffolds are typically based on fibronectin type III domain (e.g., the tenth module of the fibronectin type III (10 Fn3 domain)). The fibronectin type III domain has 7 or 8 beta strands which are distributed between two beta sheets, which themselves pack against each other to form the core of the protein, and further containing loops (analogous to CDRs) which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich, where the edge is the boundary of the protein perpendicular to the direction of the beta strands (see U.S. Pat. No. 6,818,418). Because of this structure, the non-immunoglobulin antibody mimics antigen binding properties that are similar in nature and affinity to those of antibodies. These scaffolds can be used in a loop randomization and shuffling strategy in vitro that is similar to the process of affinity maturation of antibodies in vivo. These fibronectin-based molecules can be used as scaffolds where the loop regions of the molecule can be replaced with CDRs of the invention using standard cloning techniques.

The ankyrin technology is based on using proteins with ankyrin derived repeat modules as scaffolds for bearing variable regions which can be used for binding to different targets. The ankyrin repeat module typically is a about 33 amino acid polypeptide consisting of two anti-parallel α-helices and a β-turn. Binding of the variable regions can be optimized by using ribosome display.

Avimers are used by nature for protein-protein interactions and in human over 250 proteins are structurally based on A-domains. Avimers consist of a number of different "A-domain" monomers (2-10) linked via amino acid linkers. Avimers can be created that can bind to the target antigen using the methodology described in, for example, U.S. Patent Application Publication Nos. 20040175756; 20050053973; 20050048512; and 20060008844.

Affibody affinity ligands are small, simple proteins composed of a three-helix bundle based on the scaffold of one of the IgG-binding domains of Protein A. Protein A is a surface protein from the bacterium *Staphylococcus aureus*. This scaffold domain consists of 58 amino acids, 13 of which are randomized to generate affibody libraries with a large number of ligand variants (See e.g., U.S. Pat. No. 5,831,012). Affibody molecules mimic antibodies, they have a molecular weight of 6 kDa, compared to the molecular weight of antibodies, which is 150 kDa. In spite of its small size, the binding site of affibody molecules is similar to that of an antibody.

Anticalins are known commercially, e.g., Pieris ProteoLab AG. They are derived from lipocalins, a widespread group of small and robust proteins that are usually involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Several natural lipocalins occur in human tissues or body liquids. The protein architecture is reminiscent of immunoglobulins, with hypervariable loops on top of a rigid framework. However, in contrast with antibodies or their recombinant fragments, lipocalins are composed of a single polypeptide chain with 160 to 180 amino acid residues, being just marginally bigger than a single immunoglobulin domain. The set of four loops, which makes up the binding pocket, shows pronounced structural plasticity and tolerates a variety of side chains. The binding site can thus be reshaped in a proprietary process in order to recognize prescribed target molecules of different shape with high affinity and specificity. One protein of lipocalin family, the bilin-binding protein (BBP) of *Pieris brassicae* has been used to develop anticalins by mutagenizing the set of four loops. One example of a patent application describing anticalins is in PCT Publication No. WO 199916873.

Affilin molecules are small non-immunoglobulin proteins which are designed for specific affinities towards proteins and small molecules. New affilin molecules can be very quickly selected from two libraries, each of which is based on a different human derived scaffold protein. Affilin molecules do not show any structural homology to immunoglobulin proteins. Currently, two affilin scaffolds are employed, one of which is gamma crystalline, a human structural eye lens protein and the other is "ubiquitin" superfamily proteins. Both human scaffolds are very small, show high temperature stability and are almost resistant to pH changes and denaturing agents. This high stability is mainly due to the expanded beta sheet structure of the proteins. Examples of gamma crystalline derived proteins are described in WO200104144 and examples of "ubiquitin-like" proteins are described in WO2004106368.

Protein epitope mimetics (PEM) are medium-sized, cyclic, peptide-like molecules (MW 1-2 kDa) mimicking beta-hairpin secondary structures of proteins, the major secondary structure involved in protein-protein interactions.

Domain antibodies (dAbs) can be used in the anti-TCRvb antibody molecules disclosed herein or multifunctional formats thereof are small functional binding fragments of antibodies, corresponding to the variable regions of either the heavy or light chains of antibodies. Domain antibodies are well expressed in bacterial, yeast, and mammalian cell systems. Further details of domain antibodies and methods of production thereof are known in the art (see, for example, U.S. Pat. Nos. 6,291,158; 6,582,915; 6,593,081; 6,172,197; 6,696,245; European Patents 0368684 & 0616640; WO05/035572, WO04/101790, WO04/081026, WO04/058821, WO04/003019 and WO03/002609. Nanobodies are derived from the heavy chains of an antibody.

A nanobody typically comprises a single variable domain and two constant domains (CH2 and CH3) and retains antigen-binding capacity of the original antibody. Nanobodies can be prepared by methods known in the art (See e.g., U.S. Pat. Nos. 6,765,087, 6,838,254, WO 06/079372). Unibodies consist of one light chain and one heavy chain of an IgG4 antibody. Unibodies may be made by the removal of the hinge region of IgG4 antibodies. Further details of unibodies and methods of preparing them may be found in WO2007/059782.

Tumor Antigen Moiety

In an aspect, provided herein is a multispecific molecule, e.g., a bispecific molecule, comprising:

(i) a first moiety (e.g., a first immune cell engager) comprising the anti-TCRβV antibody molecule described herein; and

(ii) a second moiety comprising one or more of: a tumor-targeting moiety; a second immune cell engager; a cytokine molecule or a stromal modifying moiety.

In some embodiments of any of the compositions or methods disclosed herein, the tumor-targeting moiety is an

antigen, e.g., a cancer antigen. In some embodiments, the cancer antigen is a tumor antigen or stromal antigen, or a hematological antigen.

In some embodiments of any of the compositions or methods disclosed herein, the tumor-targeting moiety, e.g., cancer antigen, is chosen from: BCMA, FcRH5, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD99, CD123, FcRH5, CLEC12, CD179A, SLAMF7, or NY-ESO1, PDL1, CD47, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PMSA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, MC1R, β-catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, MUC-1, CA-125, BAGE, GAGE, NY-ESO-1, 13-catenin, CDK4, CDC27, a actinin-4, TRP1/gp75, TRP2, gp100, Melan-A/MART1, gangliosides, WT1, EphA3, Epidermal growth factor receptor (EGFR), MART-2, MART-1, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RUI1, RUI2, SAGE, TRG, TRP1, TSTA, Folate receptor alpha, L1-CAM, CAIX, gpA33, GD3, GM2, VEGFR, Intergrins (Integrin alphaVbeta3, Integrin alpha5Beta1), Carbohydrates (Le), IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, (FAP), TGF-beta, hyaluronic acid, collagen, e.g., collagen IV, tenascin C, or tenascin W. In some embodiments, the tumor-targeting moiety, e.g., cancer antigen, is BCMA. In some embodiments, the tumor-targeting moiety, e.g., cancer antigen, is FcRH5.

FcRH5 Targeting Moieties

In some embodiments, the multispecific molecules disclosed herein include a targeting moiety that binds to FcRH5 (e.g., a FcRH5 targeting moiety). The FcRH5 targeting moiety can be chosen from an antibody molecule (e.g., an antigen binding domain as described herein), a receptor or a receptor fragment, or a ligand or a ligand fragment, or a combination thereof. In some embodiments, the FcRH5 targeting moiety associates with, e.g., binds to, a cancer or hematopoietic cell (e.g., a molecule, e.g., antigen, present on the surface of the cancer or hematopoietic cell). In certain embodiments, the FcRH5 targeting moiety targets, e.g., directs the multispecific molecules disclosed herein to a cancer or hematopoietic cell. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma.

In some embodiments, the multispecific molecule, e.g., the FcRH5 targeting moiety, binds to a FcRH5 antigen on the surface of a cell, e.g., a cancer or hematopoietic cell. The FcRH5 antigen can be present on a primary tumor cell, or a metastatic lesion thereof. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma. For example, the FcRH5 antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium.

The multispecific molecules described herein includes a FcRH5 targeting moiety that comprises an anti-FcRH5 antibody or antigen-binding fragment thereof described in U.S. Pat. No. 7,999,077, US20150098900, U.S. Pat. Nos. 8,299,220, 7,105,149, 8,362,213, 8,466,260, 8,617,559, US20160368985, US20150166661, and US20080247944, the entire contents of any of the aforesaid publications are herein incorporated by reference.

In some embodiments, the multispecific molecules described herein includes a FcRH5 targeting moiety that comprises an anti-FcRH5 antibody or antigen-binding fragment thereof described in U.S. Pat. No. 7,999,077, the entire contents of which are herein incorporated by reference.

BCMA Targeting Moieties

In certain embodiments, the multispecific molecules disclosed herein include a targeting moiety that binds to BCMA (e.g., a BCMA targeting moiety). The BCMA targeting moiety can be chosen from an antibody molecule (e.g., an antigen binding domain as described herein), a receptor or a receptor fragment, or a ligand or a ligand fragment, or a combination thereof. In some embodiments, the BCMA targeting moiety associates with, e.g., binds to, a cancer or hematopoietic cell (e.g., a molecule, e.g., antigen, present on the surface of the cancer or hematopoietic cell). In certain embodiments, the BCMA targeting moiety targets, e.g., directs the multispecific molecules disclosed herein to a cancer or hematopoietic cell. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma.

In some embodiments, the multispecific molecule, e.g., the BCMA targeting moiety, binds to a BCMA antigen on the surface of a cell, e.g., a cancer or hematopoietic cell. The BCMA antigen can be present on a primary tumor cell, or a metastatic lesion thereof. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma. For example, the BCMA antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium.

Exemplary BCMA Targeting Moieties

The multispecific molecules described herein can include a BCMA targeting moiety that comprises an anti-BCMA antibody or antigen-binding fragment thereof described in U.S. Pat. Nos. 8,920,776, 9,243,058, 9,340,621, 8,846,042, 7,083,785, 9,545,086, 7,276,241, 9,034,324, 7,799,902, 9,387,237, 8,821,883, US861745, US20130273055, US20160176973, US20150368351, US20150376287, US20170022284, US20160015749, US20140242077, US20170037128, US20170051068, US20160368988, US20160311915, US20160131654, US20120213768, US20110177093, US20160297885, EP3137500, EP2699259, EP2982694, EP3029068, EP3023437, WO2016090327, WO2017021450, WO2016110584, WO2016118641, WO2016168149, the entire contents of which are incorporated herein by reference.

In one embodiment, the BCMA-targeting moiety includes an antibody molecule (e.g., Fab or scFv) that binds to BCMA. In some embodiments, the antibody molecule to BCMA comprises one, two, or three CDRs from any of the heavy chain variable domain sequences of Table 1, or a closely related CDR, e.g., CDRs which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) from any of the CDR sequences of Table 14. In some embodiments, the antibody molecule to BCMA comprises a heavy chain variable domain sequence chosen from any of the amino acid sequences of Table 14, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions)).

Alternatively, or in combination with the heavy chain to BCMA disclosed herein, the antibody molecule to BCMA comprises one, two, or three CDRs from any of the light chain variable domain sequences of Table 14, or a closely related CDR, e.g., CDRs which have at least one amino acid alteration, but not more than two, three or four alterations

(e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) from any of the CDR sequences of Table 14. In some embodiments, the antibody molecule to BCMA comprises a light chain variable domain sequence chosen from any of the amino acid sequences of Table 14, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions)).

TABLE 14

Amino acid sequences of exemplary variable regions of anti-BCMA antibodies.

SEQ ID NO	Description	Sequence
3439	83A10 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CAKVLGWFDYWGQGTLVTVSS
3440	83A10 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGYPPDF TFGQGTKVEIK
3441	17A5 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CAKVAPYFAPFDYWGQGTLVTVSS
3442	17A5 VL	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLI YGASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGNPPLY TFGQGTKVEIK
3443	13A4 VH	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEW MGIIYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYC ARNGYLGDYWGQGTLVTVSS
3444	13A4 VL	DIVMTQSPLSLPVTPGEPASISCRSSQSLLHSNGYNYLDWYLQKPGQSP QLLIYLGSNRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQAM QIPTFGQGTKVEIK
3445	J22.9-xi VH	QVQLQQSGGGLVQPGGSLKLSCAASGIDFSRYWMSWVRRAPGKGLE WIGEINPDSSTINYAPSLKDKFIISRDNAKNTLYLQMSKVRSEDTALYY CASLYYDYGDAMDYWGQGTSVTVSS
3446	J22.9-xi VL	DIVMTQSQRFMTTSVGDRVSVTCKASQSVDSNVAWYQQKPRQSPKAL IFSASLRFSGVPARFTGSGSGTDFTLTISNLQSEDLAEYFCQQYNNYPLT FGAGTKLELKR
3447	2A1 VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFGDYALSWFRQAPGKGLEW VGVSRSKAYGGTTDYAASVKGRFTISRDDSKSTAYLQMNSLKTEDTA VYYCASSGYSSGWTPFDYWGQGTLVTVSS
3448	2A1 VL	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQLPGTAPKLLIF NYHQRPSGVPDRFSGSKSGSSASLAISGLQSEDEADYYCAAWDDSLNG WVFGGGTKLTVLG

CDR-Grafted Scaffolds

In embodiments, the antibody molecule is a CDR-grafted scaffold domain. In embodiments, the scaffold domain is based on a fibronectin domain, e.g., fibronectin type III domain. The overall fold of the fibronectin type III (Fn3) domain is closely related to that of the smallest functional antibody fragment, the variable domain of the antibody heavy chain. There are three loops at the end of Fn3; the positions of BC, DE and FG loops approximately correspond to those of CDR1, 2 and 3 of the VH domain of an antibody. Fn3 does not have disulfide bonds; and therefore Fn3 is stable under reducing conditions, unlike antibodies and their fragments (see, e.g., WO 98/56915; WO 01/64942; WO 00/34784). An Fn3 domain can be modified (e.g., using CDRs or hypervariable loops described herein) or varied, e.g., to select domains that bind to an antigen/marker/cell described herein.

In embodiments, a scaffold domain, e.g., a folded domain, is based on an antibody, e.g., a "minibody" scaffold created by deleting three beta strands from a heavy chain variable domain of a monoclonal antibody (see, e.g., Tramontano et al., 1994, J Mol. Recognit. 7:9; and Martin et al., 1994, EMBO J. 13:5303-5309). The "minibody" can be used to present two hypervariable loops. In embodiments, the scaffold domain is a V-like domain (see, e.g., Coia et al. WO 99/45110) or a domain derived from tendamistatin, which is a 74 residue, six-strand beta sheet sandwich held together by two disulfide bonds (see, e.g., McConnell and Hoess, 1995, J Mol. Biol. 250:460). For example, the loops of tendamistatin can be modified (e.g., using CDRs or hypervariable loops) or varied, e.g., to select domains that bind to a marker/antigen/cell described herein. Another exemplary scaffold domain is a beta-sandwich structure derived from the extracellular domain of CTLA-4 (see, e.g., WO 00/60070).

Other exemplary scaffold domains include but are not limited to T-cell receptors; MHC proteins; extracellular domains (e.g., fibronectin Type III repeats, EGF repeats); protease inhibitors (e.g., Kunitz domains, ecotin, BPTI, and so forth); TPR repeats; trifoil structures; zinc finger domains; DNA-binding proteins; particularly monomeric DNA binding proteins; RNA binding proteins; enzymes, e.g., proteases (particularly inactivated proteases), RNase; chaperones, e.g., thioredoxin, and heat shock proteins; and

intracellular signaling domains (such as SH2 and SH3 domains). See, e.g., US 20040009530 and U.S. Pat. No. 7,501,121, incorporated herein by reference.

In embodiments, a scaffold domain is evaluated and chosen, e.g., by one or more of the following criteria: (1) amino acid sequence, (2) sequences of several homologous domains, (3) 3-dimensional structure, and/or (4) stability data over a range of pH, temperature, salinity, organic solvent, oxidant concentration. In embodiments, the scaffold domain is a small, stable protein domain, e.g., a protein of less than 100, 70, 50, 40 or 30 amino acids. The domain may include one or more disulfide bonds or may chelate a metal, e.g., zinc.

Antibody-Based Fusions

A variety of formats can be generated which contain additional binding entities attached to the N or C terminus of antibodies. These fusions with single chain or disulfide stabilized Fvs or Fabs result in the generation of tetravalent molecules with bivalent binding specificity for each antigen. Combinations of scFvs and scFabs with IgGs enable the production of molecules which can recognize three or more different antigens.

Antibody-Fab Fusion

Antibody-Fab fusions are bispecific antibodies comprising a traditional antibody to a first target and a Fab to a second target fused to the C terminus of the antibody heavy chain. Commonly the antibody and the Fab will have a common light chain. Antibody fusions can be produced by (1) engineering the DNA sequence of the target fusion, and (2) transfecting the target DNA into a suitable host cell to express the fusion protein. It seems like the antibody-scFv fusion may be linked by a (Gly)-Ser linker between the C-terminus of the CH3 domain and the N-terminus of the scFv, as described by Coloma, J. et al. (1997) *Nature Biotech* 15:159.

Antibody-scFv Fusion

Antibody-scFv Fusions are bispecific antibodies comprising a traditional antibody and a scFv of unique specificity fused to the C terminus of the antibody heavy chain. The scFv can be fused to the C terminus through the Heavy Chain of the scFv either directly or through a linker peptide. Antibody fusions can be produced by (1) engineering the DNA sequence of the target fusion, and (2) transfecting the target DNA into a suitable host cell to express the fusion protein. It seems like the antibody-scFv fusion may be linked by a (Gly)-Ser linker between the C-terminus of the CH3 domain and the N-terminus of the scFv, as described by Coloma, J. et al. (1997) *Nature Biotech* 15:159.

Variable Domain Immunoglobulin DVD

A related format is the dual variable domain immunoglobulin (DVD), which are composed of VH and VL domains of a second specificity place upon the N termini of the V domains by shorter linker sequences.

Other exemplary multispecific antibody formats include, e.g., those described in the following US20160114057A1, US20130243775A1, US20140051833, US20130022601, US20150017187A1, US20120201746A1, US20150133638A1, US20130266568A1, US20160145340A1, WO2015127158A1, US20150203591A1, US20140322221A1, US20130303396A1, US20110293613, US20130017200A1, US20160102135A1, WO2015197598A2, WO2015197582A1, U.S. Pat. No. 9,359,437, US20150018529, WO2016115274A1, WO2016087416A1, US20080069820A1, U.S. Pat. Nos. 9,145,588B, 7,919,257, and US20150232560A1. Exemplary multispecific molecules utilizing a full antibody-Fab/scFab format include those described in the following, U.S. Pat. No. 9,382,323B2, US20140072581A1, US20140308285A1, US20130165638A1, US20130267686A1, US20140377269A1, U.S. Pat. No. 7,741,446B2, and WO1995009917A1. Exemplary multispecific molecules utilizing a domain exchange format include those described in the following, US20150315296A1, WO2016087650A1, US20160075785A1, WO2016016299A1, US20160130347A1, US20150166670, U.S. Pat. No. 8,703,132B2, US20100316645, U.S. Pat. No. 8,227,577B2, US20130078249.

Fc-Containing Entities (Mini-Antibodies)

Fc-containing entities, also known as mini-antibodies, can be generated by fusing scFv to the C-termini of constant heavy region domain 3 (CH3-scFv) and/or to the hinge region (scFv-hinge-Fc) of an antibody with a different specificity. Trivalent entities can also be made which have disulfide stabilized variable domains (without peptide linker) fused to the C-terminus of CH3 domains of IgGs.

Fc-Containing Multispecific Molecules

In some embodiments, the multispecific molecules disclosed herein includes an immunoglobulin constant region (e.g., an Fc region). Exemplary Fc regions can be chosen from the heavy chain constant regions of IgG1, IgG2, IgG3 or IgG4; more particularly, the heavy chain constant region of human IgG1, IgG2, IgG3, or IgG4.

In some embodiments, the immunoglobulin chain constant region (e.g., the Fc region) is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function.

In other embodiments, an interface of a first and second immunoglobulin chain constant regions (e.g., a first and a second Fc region) is altered, e.g., mutated, to increase or decrease dimerization, e.g., relative to a non-engineered interface, e.g., a naturally-occurring interface. For example, dimerization of the immunoglobulin chain constant region (e.g., the Fc region) can be enhanced by providing an Fc interface of a first and a second Fc region with one or more of: a paired protuberance-cavity ("knob-in-a hole"), an electrostatic interaction, or a strand-exchange, such that a greater ratio of heteromultimer to homomultimer forms, e.g., relative to a non-engineered interface.

In some embodiments, the multispecific molecules include a paired amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1 For example, the immunoglobulin chain constant region (e.g., Fc region) can include a paired an amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), and T366W (e.g., corresponding to a protuberance or knob).

In other embodiments, the multifunctional molecule includes a half-life extender, e.g., a human serum albumin or an antibody molecule to human serum albumin.

Heterodimerized Antibody Molecules & Methods of Making

Various methods of producing multispecific antibodies have been disclosed to address the problem of incorrect heavy chain pairing. Exemplary methods are described below. Exemplary multispecific antibody formats and methods of making said multispecific antibodies are also disclosed in e.g., Speiss et al. Molecular Immunology 67 (2015) 95-106; and Klein et al mAbs 4:6, 653-663; November/December 2012; the entire contents of each of which are incorporated by reference herein.

Heterodimerized bispecific antibodies are based on the natural IgG structure, wherein the two binding arms recognize different antigens. IgG derived formats that enable defined monovalent (and simultaneous) antigen binding are generated by forced heavy chain heterodimerization, combined with technologies that minimize light chain mispairing (e.g., common light chain). Forced heavy chain heterodimerization can be obtained using, e.g., knob-in-hole OR strand exchange engineered domains (SEED).

Knob-in-Hole

Knob-in-Hole as described in U.S. Pat. Nos. 5,731,116, 7,476,724 and Ridgway, J. et al. (1996) Prot. Engineering 9(7): 617-621, broadly involves: (1) mutating the CH3 domain of one or both antibodies to promote heterodimerization; and (2) combining the mutated antibodies under conditions that promote heterodimerization. "Knobs" or "protuberances" are typically created by replacing a small amino acid in a parental antibody with a larger amino acid (e.g., T366Y or T366W); "Holes" or "cavities" are created by replacing a larger residue in a parental antibody with a smaller amino acid (e.g., Y407T, T366S, L368A and/or Y407V).

For bispecific antibodies including an Fc domain, introduction of specific mutations into the constant region of the heavy chains to promote the correct heterodimerization of the Fc portion can be utilized. Several such techniques are reviewed in Klein et al. (mAbs (2012) 4:6, 1-11), the contents of which are incorporated herein by reference in their entirety. These techniques include the "knobs-into-holes" (KiH) approach which involves the introduction of a bulky residue into one of the CH3 domains of one of the antibody heavy chains. This bulky residue fits into a complementary "hole" in the other CH3 domain of the paired heavy chain so as to promote correct pairing of heavy chains (see e.g., U.S. Pat. No. 7,642,228).

Exemplary KiH mutations include S354C, T366W in the "knob" heavy chain and Y349C, T366S, L368A, Y407V in the "hole" heavy chain. Other exemplary KiH mutations are provided in Table 4, with additional optional stabilizing Fc cysteine mutations.

TABLE 4

Exemplary Fc KiH mutations and optional Cysteine mutations		
Position	Knob Mutation	Hole Mutation
T366	T366W	T366S
L368	—	L368A
Y407	—	Y407V
Additional Cysteine Mutations to form a stabilizing disulfide bridge		
Position	Knob CH3	Hole CH3
S354	S354C	—
Y349	—	Y349C

Other Fc mutations are provided by Igawa and Tsunoda who identified 3 negatively charged residues in the CH3 domain of one chain that pair with three positively charged residues in the CH3 domain of the other chain. These specific charged residue pairs are: E356-K439, E357-K370, D399-K409 and vice versa. By introducing at least two of the following three mutations in chain A: E356K, E357K and D399K, as well as K370E, K409D, K439E in chain B, alone or in combination with newly identified disulfide bridges, they were able to favor very efficient heterodimerization while suppressing homodimerization at the same time (Martens T et al. A novel one-armed antic-Met antibody inhibits glioblastoma growth in vivo. Clin Cancer Res 2006; 12:6144-52; PMID:17062691). Xencor defined 41 variant pairs based on combining structural calculations and sequence information that were subsequently screened for maximal heterodimerization, defining the combination of S364H, F405A (HA) on chain A and Y349T, T394F on chain B (TF) (Moore G L et al. A novel bispecific antibody format enables simultaneous bivalent and monovalent co-engagement of distinct target antigens. MAbs 2011; 3:546-57; PMID: 22123055).

Other exemplary Fc mutations to promote heterodimerization of multispecific antibodies include those described in the following references, the contents of each of which is incorporated by reference herein, WO2016071377A1, US20140079689A1, US20160194389A1, US20160257763, WO2016071376A2, WO2015107026A1, WO2015107025A1, WO2015107015A1, US20150353636A1, US20140199294A1, U.S. Pat. No. 7,750,128B2, US20160229915A1, US20150344570A1, U.S. Pat. No. 8,003,774A1, US20150337049A1, US20150175707A1, US20140242075A1, US20130195849A1, US20120149876A1, US20140200331A1, U.S. Pat. No. 9,309,311B2, U.S. Pat. No. 8,586,713, US20140037621A1, US20130178605A1, US20140363426A1, US20140051835A1 and US20110054151A1.

Stabilizing cysteine mutations have also been used in combination with KiH and other Fc heterodimerization promoting variants, see e.g., U.S. Pat. No. 7,183,076. Other exemplary cysteine modifications include, e.g., those disclosed in US20140348839A1, U.S. Pat. No. 7,855,275B2, and U.S. Pat. No. 9,000,130B2.

Strand Exchange Engineered Domains (SEED)

Heterodimeric Fc platform that support the design of bispecific and asymmetric fusion proteins by devising strand-exchange engineered domain (SEED) C(H)3 heterodimers are known. These derivatives of human IgG and IgA C(H)3 domains create complementary human SEED C(H)3 heterodimers that are composed of alternating segments of human IgA and IgG C(H)3 sequences. The resulting pair of SEED C(H)3 domains preferentially associates to form heterodimers when expressed in mammalian cells. SEEDbody (Sb) fusion proteins consist of [IgG1 hinge]-C(H)2-[SEED C(H)3], that may be genetically linked to one or more fusion partners (see e.g., Davis J H et al. SEEDbodies: fusion proteins based on strand exchange engineered domain (SEED) CH3 heterodimers in an Fc analogue platform for asymmetric binders or immunofusions and bispecific antibodies. Protein Eng Des Sel 2010; 23:195-202; PMID:20299542 and U.S. Pat. No. 8,871,912. The contents of each of which are incorporated by reference herein).

Duobody

"Duobody" technology to produce bispecific antibodies with correct heavy chain pairing are known. The DuoBody technology involves three basic steps to generate stable bispecific human IgG1 antibodies in a post-production exchange reaction. In a first step, two IgG1s, each containing single matched mutations in the third constant (CH3) domain, are produced separately using standard mammalian recombinant cell lines. Subsequently, these IgG1 antibodies are purified according to standard processes for recovery and purification. After production and purification (post-production), the two antibodies are recombined under tailored laboratory conditions resulting in a bispecific antibody product with a very high yield (typically >95%) (see e.g., Labrijn et al, PNAS 2013; 110(13):5145-5150 and Labrijn et al.

Nature Protocols 2014; 9(10):2450-63, the contents of each of which are incorporated by reference herein).

Electrostatic Interactions

Methods of making multispecific antibodies using CH3 amino acid changes with charged amino acids such that homodimer formation is electrostatically unfavorable are disclosed. EP1870459 and WO 2009089004 describe other strategies for favoring heterodimer formation upon co-expression of different antibody domains in a host cell. In these methods, one or more residues that make up the heavy chain constant domain 3 (CH3), CH3-CH3 interfaces in both CH3 domains are replaced with a charged amino acid such that homodimer formation is electrostatically unfavorable and heterodimerization is electrostatically favorable. Additional methods of making multispecific molecules using electrostatic interactions are described in the following references, the contents of each of which is incorporated by reference herein, include US20100015133, U.S. Pat. No. 8,592,562B2, U.S. Pat. No. 9,200,060B2, US20140154254A1, and U.S. Pat. No. 9,358,286A1.

Common Light Chain

Light chain mispairing needs to be avoided to generate homogenous preparations of bispecific IgGs. One way to achieve this is through the use of the common light chain principle, i.e. combining two binders that share one light chain but still have separate specificities. An exemplary method of enhancing the formation of a desired bispecific antibody from a mixture of monomers is by providing a common variable light chain to interact with each of the heteromeric variable heavy chain regions of the bispecific antibody. Compositions and methods of producing bispecific antibodies with a common light chain as disclosed in, e.g., U.S. Pat. No. 7,183,076B2, US20110177073A1, EP2847231A1, WO2016079081A1, and EP3055329A1, the contents of each of which is incorporated by reference herein.

CrossMab

Another option to reduce light chain mispairing is the CrossMab technology which avoids non-specific L chain mispairing by exchanging CH1 and CL domains in the Fab of one half of the bispecific antibody. Such crossover variants retain binding specificity and affinity, but make the two arms so different that L chain mispairing is prevented. The CrossMab technology (as reviewed in Klein et al. Supra) involves domain swapping between heavy and light chains so as to promote the formation of the correct pairings. Briefly, to construct a bispecific IgG-like CrossMab antibody that could bind to two antigens by using two distinct light chain-heavy chain pairs, a two-step modification process is applied. First, a dimerization interface is engineered into the C-terminus of each heavy chain using a heterodimerization approach, e.g., Knob-into-hole (KiH) technology, to ensure that only a heterodimer of two distinct heavy chains from one antibody (e.g., Antibody A) and a second antibody (e.g., Antibody B) is efficiently formed. Next, the constant heavy 1 (CH1) and constant light (CL) domains of one antibody are exchanged (Antibody A), keeping the variable heavy (VH) and variable light (VL) domains consistent. The exchange of the CH1 and CL domains ensured that the modified antibody (Antibody A) light chain would only efficiently dimerize with the modified antibody (antibody A) heavy chain, while the unmodified antibody (Antibody B) light chain would only efficiently dimerize with the unmodified antibody (Antibody B) heavy chain; and thus only the desired bispecific CrossMab would be efficiently formed (see e.g., Cain, C. SciBX 4(28); doi:10.1038/scibx.2011.783, the contents of which are incorporated by reference herein).

Common Heavy Chain

An exemplary method of enhancing the formation of a desired bispecific antibody from a mixture of monomers is by providing a common variable heavy chain to interact with each of the heteromeric variable light chain regions of the bispecific antibody. Compositions and methods of producing bispecific antibodies with a common heavy chain are disclosed in, e.g., US20120184716, US20130317200, and US20160264685A1, the contents of each of which is incorporated by reference herein.

Amino Acid Modifications

Alternative compositions and methods of producing multispecific antibodies with correct light chain pairing include various amino acid modifications. For example, Zymeworks describes heterodimers with one or more amino acid modifications in the CH1 and/or CL domains, one or more amino acid modifications in the VH and/or VL domains, or a combination thereof, which are part of the interface between the light chain and heavy chain and create preferential pairing between each heavy chain and a desired light chain such that when the two heavy chains and two light chains of the heterodimer pair are co-expressed in a cell, the heavy chain of the first heterodimer preferentially pairs with one of the light chains rather than the other (see e.g., WO2015181805). Other exemplary methods are described in WO2016026943 (Argen-X), US20150211001, US20140072581A1, US20160039947A1, and US20150368352.

Lambda/Kappa Formats

Multispecific molecules (e.g., multispecific antibody molecules) that include the lambda light chain polypeptide and a kappa light chain polypeptides, can be used to allow for heterodimerization. Methods for generating bispecific antibody molecules comprising the lambda light chain polypeptide and a kappa light chain polypeptides are disclosed in PCT/US17/53053 filed on Sep. 22, 2017 and designated publication number WO 2018/057955, incorporated herein by reference in its entirety.

In embodiments, the multispecific molecule includes a multispecific antibody molecule, e.g., an antibody molecule comprising two binding specificities, e.g., a bispecific antibody molecule. The multispecific antibody molecule includes:

- a lambda light chain polypeptide 1 (LLCP1) specific for a first epitope;
- a heavy chain polypeptide 1 (HCP1) specific for the first epitope;
- a kappa light chain polypeptide 2 (KLCP2) specific for a second epitope; and
- a heavy chain polypeptide 2 (HCP2) specific for the second epitope.

"Lambda light chain polypeptide 1 (LLCP1)", as that term is used herein, refers to a polypeptide comprising sufficient light chain (LC) sequence, such that when combined with a cognate heavy chain variable region, can mediate specific binding to its epitope and complex with an HCP1. In an embodiment it comprises all or a fragment of a CH1 region. In an embodiment, an LLCP1 comprises LC-CDR1, LC-CDR2, LC-CDR3, FR1, FR2, FR3, FR4, and CH1, or sufficient sequence therefrom to mediate specific binding of its epitope and complex with an HCP1. LLCP1, together with its HCP1, provide specificity for a first epitope (while KLCP2, together with its HCP2, provide specificity

for a second epitope). As described elsewhere herein, LLCP1 has a higher affinity for HCP1 than for HCP2.

"Kappa light chain polypeptide 2 (KLCP2)", as that term is used herein, refers to a polypeptide comprising sufficient light chain (LC) sequence, such that when combined with a cognate heavy chain variable region, can mediate specific binding to its epitope and complex with an HCP2. In some embodiments, it comprises all or a fragment of a CH1 region. In an embodiment, a KLCP2 comprises LC-CDR1, LC-CDR2, LC-CDR3, FR1, FR2, FR3, FR4, and CH1, or sufficient sequence therefrom to mediate specific binding of its epitope and complex with an HCP2. KLCP2, together with its HCP2, provide specificity for a second epitope (while LLCP1, together with its HCP1, provide specificity for a first epitope).

"Heavy chain polypeptide 1 (HCP1)", as that term is used herein, refers to a polypeptide comprising sufficient heavy chain (HC) sequence, e.g., HC variable region sequence, such that when combined with a cognate LLCP1, can mediate specific binding to its epitope and complex with an HCP1. In some embodiments, it comprises all or a fragment of a CH1region. In an embodiment, it comprises all or a fragment of a CH2 and/or CH3 region. In an embodiment an HCP1 comprises HC-CDR1, HC-CDR2, HC-CDR3, FR1, FR2, FR3, FR4, CH1, CH2, and CH3, or sufficient sequence therefrom to: (i) mediate specific binding of its epitope and complex with an LLCP1, (ii) to complex preferentially, as described herein to LLCP1 as opposed to KLCP2; and (iii) to complex preferentially, as described herein, to an HCP2, as opposed to another molecule of HCP1. HCP1, together with its LLCP1, provide specificity for a first epitope (while KLCP2, together with its HCP2, provide specificity for a second epitope).

"Heavy chain polypeptide 2 (HCP2)", as that term is used herein, refers to a polypeptide comprising sufficient heavy chain (HC) sequence, e.g., HC variable region sequence, such that when combined with a cognate LLCP1, can mediate specific binding to its epitope and complex with an HCP1. In some embodiments, it comprises all or a fragment of a CH1region. In some embodiments, it comprises all or a fragment of a CH2 and/or CH3 region. In an embodiment an HCP1 comprises HC-CDR1, HC-CDR2, HC-CDR3, FR1, FR2, FR3, FR4, CH1, CH2, and CH3, or sufficient sequence therefrom to: (i) mediate specific binding of its epitope and complex with an KLCP2, (ii) to complex preferentially, as described herein to KLCP2 as opposed to LLCP1; and (iii) to complex preferentially, as described herein, to an HCP1, as opposed to another molecule of HCP2. HCP2, together with its KLCP2, provide specificity for a second epitope (while LLCP1, together with its HCP1, provide specificity for a first epitope).

In some embodiments of the multispecific antibody molecule disclosed herein: LLCP1 has a higher affinity for HCP1 than for HCP2; and/or KLCP2 has a higher affinity for HCP2 than for HCP1.

In embodiments, the affinity of LLCP1 for HCP1 is sufficiently greater than its affinity for HCP2, such that under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions, at least 75, 80, 90, 95, 98, 99, 99.5, or 99.9% of the multispecific antibody molecule molecules have a LLCP1complexed, or interfaced with, a HCP.

In some embodiments of the multispecific antibody molecule disclosed herein:

the HCP1 has a greater affinity for HCP2, than for a second molecule of HCP1; and/or

the HCP2 has a greater affinity for HCP1, than for a second molecule of HCP2.

In embodiments, the affinity of HCP1 for HCP2 is sufficiently greater than its affinity for a second molecule of HCP1, such that under preselected conditions, e.g., in aqueous buffer, e.g., at pH 7, in saline, e.g., at pH 7, or under physiological conditions, at least 75%, 80, 90, 95, 98, 99 99.5 or 99.9% of the multispecific antibody molecule molecules have a HCP1complexed, or interfaced with, a HCP2.

In another aspect, disclosed herein is a method for making, or producing, a multispecific antibody molecule. The method includes:

(i) providing a first heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH), a first CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both));

(ii) providing a second heavy chain polypeptide (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both));

(iii) providing a lambda chain polypeptide (e.g., a lambda light variable region (VLλ), a lambda light constant chain (VLλ), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH); and

(iv) providing a kappa chain polypeptide (e.g., a lambda light variable region (VLκ), a lambda light constant chain (VLκ), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH),

under conditions where (i)-(iv) associate.

In embodiments, the first and second heavy chain polypeptides form an Fc interface that enhances heterodimerization.

In embodiments, (i)-(iv) (e.g., nucleic acid encoding (i)-(iv)) are introduced in a single cell, e.g., a single mammalian cell, e.g., a CHO cell. In embodiments, (i)-(iv) are expressed in the cell.

In embodiments, (i)-(iv) (e.g., nucleic acid encoding (i)-(iv)) are introduced in different cells, e.g., different mammalian cells, e.g., two or more CHO cell. In embodiments, (i)-(iv) are expressed in the cells.

In embodiments, the method further comprises purifying a cell-expressed antibody molecule, e.g., using a lambda- and/or- kappa-specific purification, e.g., affinity chromatography.

In embodiments, the method further comprises evaluating the cell-expressed multispecific antibody molecule. For example, the purified cell-expressed multispecific antibody molecule can be analyzed by techniques known in the art, include mass spectrometry. In one embodiment, the purified cell-expressed antibody molecule is cleaved, e.g., digested with papain to yield the Fab moieties and evaluated using mass spectrometry.

In embodiments, the method produces correctly paired kappa/lambda multispecific, e.g., bispecific, antibody molecules in a high yield, e.g., at least 75%, 80, 90, 95, 98, 99 99.5 or 99.9%.

In other embodiments, the multispecific, e.g., a bispecific, antibody molecule that includes:

(i) a first heavy chain polypeptide (HCP1) (e.g., a heavy chain polypeptide comprising one, two, three or all of a first heavy chain variable region (first VH), a first

CH1, a first heavy chain constant region (e.g., a first CH2, a first CH3, or both)), e.g., wherein the HCP1 binds to a first epitope;

(ii) a second heavy chain polypeptide (HCP2) (e.g., a heavy chain polypeptide comprising one, two, three or all of a second heavy chain variable region (second VH), a second CH1, a second heavy chain constant region (e.g., a second CH2, a second CH3, or both)), e.g., wherein the HCP2 binds to a second epitope;

(iii) a lambda light chain polypeptide (LLCP1) (e.g., a lambda light variable region (VL1), a lambda light constant chain (VL1), or both) that preferentially associates with the first heavy chain polypeptide (e.g., the first VH), e.g., wherein the LLCP1 binds to a first epitope; and

(iv) a kappa light chain polypeptide (KLCP2) (e.g., a lambda light variable region (VLk), a lambda light constant chain (VLk), or both) that preferentially associates with the second heavy chain polypeptide (e.g., the second VH), e.g., wherein the KLCP2 binds to a second epitope.

In embodiments, the first and second heavy chain polypeptides form an Fc interface that enhances heterodimerization. In embodiments, the multispecific antibody molecule has a first binding specificity that includes a hybrid VL1-CL1 heterodimerized to a first heavy chain variable region connected to the Fc constant, CH2-CH3 domain (having a knob modification) and a second binding specificity that includes a hybrid VLk-CLk heterodimerized to a second heavy chain variable region connected to the Fc constant, CH2-CH3 domain (having a hole modification).

Cytokine Molecules

Cytokines are generally polypeptides that influence cellular activity, for example, through signal transduction pathways. Accordingly, a cytokine of the multispecific or multifunctional polypeptide is useful and can be associated with receptor-mediated signaling that transmits a signal from outside the cell membrane to modulate a response within the cell. Cytokines are proteinaceous signaling compounds that are mediators of the immune response. They control many different cellular functions including proliferation, differentiation and cell survival/apoptosis; cytokines are also involved in several pathophysiological processes including viral infections and autoimmune diseases. Cytokines are synthesized under various stimuli by a variety of cells of both the innate (monocytes, macrophages, dendritic cells) and adaptive (T- and B-cells) immune systems. Cytokines can be classified into two groups: pro- and anti-inflammatory. Pro-inflammatory cytokines, including IFNγ, IL-1, IL-6 and TNF-alpha, are predominantly derived from the innate immune cells and Th1 cells. Anti-inflammatory cytokines, including IL-10, IL-4, IL-13 and IL-5, are synthesized from Th2 immune cells.

The present disclosure provides, inter alia, multispecific (e.g., bi-, tri-, quad-specific) or multifunctional molecules, that include, e.g., are engineered to contain, one or more cytokine molecules, e.g., immunomodulatory (e.g., proinflammatory) cytokines and variants, e.g., functional variants, thereof. Accordingly, in some embodiments, the cytokine molecule is an interleukin or a variant, e.g., a functional variant thereof. In some embodiments the interleukin is a proinflammatory interleukin. In some embodiments the interleukin is chosen from interleukin-2 (IL-2), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), interleukin-7 (IL-7), or interferon gamma. In some embodiments, the cytokine molecule is a proinflammatory cytokine.

In certain embodiments, the cytokine is a single chain cytokine. In certain embodiments, the cytokine is a multichain cytokine (e.g., the cytokine comprises 2 or more (e.g., 2) polypeptide chains. An exemplary multichain cytokine is IL-12.

Examples of useful cytokines include, but are not limited to, GM-CSF, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-21, IFN-α, IFN-γ, MIP-1α, MIP-1β, TGF-β, TNF-α, and TNFβ. In one embodiment the cytokine of the multispecific or multifunctional polypeptide is a cytokine selected from the group of GM-CSF, IL-2, IL-7, IL-8, IL-10, IL-12, IL-15, IL-21, IFN-α, IFN-γ, MIP-1α, MIP-1β and TGF-β. In one embodiment the cytokine of the i the multispecific or multifunctional polypeptide is a cytokine selected from the group of IL-2, IL-7, IL-10, IL-12, IL-15, IFN-α, and IFN-γ. In certain embodiments the cytokine is mutated to remove N- and/or O-glycosylation sites. Elimination of glycosylation increases homogeneity of the product obtainable in recombinant production.

In one embodiment, the cytokine of the multispecific or multifunctional polypeptide is IL-2. In a specific embodiment, the IL-2 cytokine can elicit one or more of the cellular responses selected from the group consisting of: proliferation in an activated T lymphocyte cell, differentiation in an activated T lymphocyte cell, cytotoxic T cell (CTL) activity, proliferation in an activated B cell, differentiation in an activated B cell, proliferation in a natural killer (NK) cell, differentiation in a NK cell, cytokine secretion by an activated T cell or an NK cell, and NK/lymphocyte activated killer (LAK) antitumor cytotoxicity. In another particular embodiment the IL-2 cytokine is a mutant IL-2 cytokine having reduced binding affinity to the .alpha.-subunit of the IL-2 receptor. Together with the .beta.- and .gamma.-subunits (also known as CD122 and CD132, respectively), the .alpha.-subunit (also known as CD25) forms the heterotrimeric high-affinity IL-2 receptor, while the dimeric receptor consisting only of the β- and γ-subunits is termed the intermediate-affinity IL-2 receptor. As described in PCT patent application number PCT/EP2012/051991, which is incorporated herein by reference in its entirety, a mutant IL-2 polypeptide with reduced binding to the .alpha.-subunit of the IL-2 receptor has a reduced ability to induce IL-2 signaling in regulatory T cells, induces less activation-induced cell death (AICD) in T cells, and has a reduced toxicity profile in vivo, compared to a wild-type IL-2 polypeptide. The use of such an cytokine with reduced toxicity is particularly advantageous in a multispecific or multifunctional polypeptide according to the invention, having a long serum half-life due to the presence of an Fc domain. In one embodiment, the mutant IL-2 cytokine of the multispecific or multifunctional polypeptide according to the invention comprises at least one amino acid mutation that reduces or abolishes the affinity of the mutant IL-2 cytokine to the .alpha.-subunit of the IL-2 receptor (CD25) but preserves the affinity of the mutant IL-2 cytokine to the intermediate-affinity IL-2 receptor (consisting of the β and γ subunits of the IL-2 receptor), compared to the non-mutated IL-2 cytokine. In one embodiment the one or more amino acid mutations are amino acid substitutions. In a specific embodiment, the mutant IL-2 cytokine comprises one, two or three amino acid substitutions at one, two or three position(s) selected from the positions corresponding to residue 42, 45, and 72 of human IL-2. In a more specific embodiment, the mutant IL-2 cytokine comprises three amino acid substitutions at the positions corresponding to residue 42, 45 and 72 of human IL-2. In an even more specific embodiment, the mutant IL-2 cytokine is human

IL-2 comprising the amino acid substitutions F42A, Y45A and L72G. In one embodiment the mutant IL-2 cytokine additionally comprises an amino acid mutation at a position corresponding to position 3 of human IL-2, which eliminates the O-glycosylation site of IL-2. Particularly, said additional amino acid mutation is an amino acid substitution replacing a threonine residue by an alanine residue. A particular mutant IL-2 cytokine useful in the invention comprises four amino acid substitutions at positions corresponding to residues 3, 42, 45 and 72 of human IL-2. Specific amino acid substitutions are T3A, F42A, Y45A and L72G. As demonstrated in PCT patent application number PCT/EP2012/051991 and in the appended Examples, said quadruple mutant IL-2 polypeptide (IL-2 qm) exhibits no detectable binding to CD25, reduced ability to induce apoptosis in T cells, reduced ability to induce IL-2 signaling in T.sub.reg cells, and a reduced toxicity profile in vivo. However, it retains ability to activate IL-2 signaling in effector cells, to induce proliferation of effector cells, and to generate IFN-γ as a secondary cytokine by NK cells.

The IL-2 or mutant IL-2 cytokine according to any of the above embodiments may comprise additional mutations that provide further advantages such as increased expression or stability. For example, the cysteine at position 125 may be replaced with a neutral amino acid such as alanine, to avoid the formation of disulfide-bridged IL-2 dimers. Thus, in certain embodiments the IL-2 or mutant IL-2 cytokine of the multispecific or multifunctional polypeptide according to the invention comprises an additional amino acid mutation at a position corresponding to residue 125 of human IL-2. In one embodiment said additional amino acid mutation is the amino acid substitution C125A.

In a specific embodiment the IL-2 cytokine of the multispecific or multifunctional polypeptide comprises the polypeptide sequence of SEQ ID NO: 2270 [APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTFKFYMPKKATELKHLQCL EEELKPLEEVLNLAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLNR WITFAQSIISTLT].

In another specific embodiment the IL-2 cytokine of the multispecific or multifunctional polypeptide comprises the polypeptide sequence of SEQ ID NO: 2280 [APASSSTKKTQLQLEHLLLDLQMILNGINNYKNPKLTRMLTAKFAMPKKATELKHLQC LEEELKPLEEVLNGAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYADETATIVEFLN RWITFAQSIISTLT].

In another embodiment the cytokine of the multispecific or multifunctional polypeptide is IL-12. In a specific embodiment said IL-12 cytokine is a single chain IL-12 cytokine. In an even more specific embodiment the single chain IL-12 cytokine comprises the polypeptide sequence of SEQ ID NO: 2290 [IWELKKDVYVVELDWYPDAPGEMVVLTCDTPEEDGITWTLDQSSEVLGSGKTLTIQVK EFGDAGQYTCHKGGEVLSHSLLLLHKKEDGIWSTDILKDQKEPKNKTFLRCEAKNYSGR FTCWWLTTISTDLTFSVKSSRGSSDPQGVTCGAATLSAERVRGDNKEYEYSVECQEDSA CPAAEESLPIEVMVDAVHKLKYENYTSSFFIRDIIKPDPPKNLQLKPLKNSRQVEVSWEY PDTWSTPHSYFSLTFCVQVQGKSKREKKDRVFTDKTSATVICRKNASISVRAQDRYYSS SWSEWASVPCSGGGGSGGGGSGGGGSRNLPVATPDPGMFPCLHHSQNLLRAVSNMLQ KARQTLEFYPCTSEEIDHEDITKDKTSTVEACLPLELTKNESCLNSRETSFITNGSCLASRK TSFMMALCLSSIYEDLKMYQVEFKTMNAKLLMDPKRQIFLDQNMLAVIDELMQALNFN SETVPQKSSLEEPDFYKTKIKLCILLHAFRIRAVTIDRVMSYLNAS].

In one embodiment, the IL-12 cytokine can elicit one or more of the cellular responses selected from the group consisting of: proliferation in a NK cell, differentiation in a NK cell, proliferation in a T cell, and differentiation in a T cell.

In another embodiment the cytokine of the multispecific or multifunctional polypeptide is IL-10. In a specific embodiment said IL-10 cytokine is a single chain IL-10 cytokine. In an even more specific embodiment the single chain IL-10 cytokine comprises the polypeptide sequence of SEQ ID NO: 2300 [SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKG YLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENK SKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRNGGGGSGGGGSGGGGS GGGGSSPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLE DFKGYLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLP CENKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN].

In another specific embodiment the IL-10 cytokine is a monomeric IL-10 cytokine. In a more specific embodiment the monomeric IL-10 cytokine comprises the polypeptide sequence of SEQ ID NO: 2310 [SPGQGTQSENSCTHFPGNLPNMLRDLRDAFSRVKTFFQMKDQLDNLLLKESLLEDFKG YLGCQALSEMIQFYLEEVMPQAENQDPDIKAHVNSLGENLKTLRLRLRRCHRFLPCENG GGSGGKSKAVEQVKNAFNKLQEKGIYKAMSEFDIFINYIEAYMTMKIRN].

In one embodiment, the IL-10 cytokine can elicit one or more of the cellular responses selected from the group consisting of: inhibition of cytokine secretion, inhibition of antigen presentation by antigen presenting cells, reduction of oxygen radical release, and inhibition of T cell proliferation. A multispecific or multifunctional polypeptide according to the invention wherein the cytokine is IL-10 is particularly useful for downregulation of inflammation, e.g. in the treatment of an inflammatory disorder.

In another embodiment, the cytokine of the multispecific or multifunctional polypeptide is IL-15. In a specific embodiment said IL-15 cytokine is a mutant IL-15 cytokine having reduced binding affinity to the α-subunit of the IL-15 receptor. Without wishing to be bound by theory, a mutant IL-15 polypeptide with reduced binding to the .alpha.-subunit of the IL-15 receptor has a reduced ability to bind to fibroblasts throughout the body, resulting in improved pharmacokinetics and toxicity profile, compared to a wild-type IL-15 polypeptide. The use of an cytokine with reduced toxicity, such as the described mutant IL-2 and mutant IL-15 effector moieties, is particularly advantageous in a multispecific or multifunctional polypeptide according to the invention, having a long serum half-life due to the presence of an Fc domain. In one embodiment the mutant IL-15 cytokine of the multispecific or multifunctional polypeptide according to the invention comprises at least one amino acid mutation that reduces or abolishes the affinity of the mutant IL-15 cytokine to the .alpha.-subunit of the IL-15 receptor but preserves the affinity of the mutant IL-15 cytokine to the intermediate-affinity IL-15/IL-2 receptor (consisting of the .beta.- and .gamma.-subunits of the IL-15/IL-2 receptor), compared to the non-mutated IL-15 cytokine. In one embodiment the amino acid mutation is an amino acid

substitution. In a specific embodiment, the mutant IL-15 cytokine comprises an amino acid substitution at the position corresponding to residue 53 of human IL-15. In a more specific embodiment, the mutant IL-15 cytokine is human IL-15 comprising the amino acid substitution E53A. In one embodiment the mutant IL-15 cytokine additionally comprises an amino acid mutation at a position corresponding to position 79 of human IL-15, which eliminates the N-glycosylation site of IL-15. Particularly, said additional amino acid mutation is an amino acid substitution replacing an asparagine residue by an alanine residue. In an even more specific embodiment the IL-15 cytokine comprises the polypeptide sequence of SEQ ID NO: 2320 [NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLASGDASIH DTVENLIILANNSLSSNGAVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS]. In one embodiment, the IL-15 cytokine can elicit one or more of the cellular responses selected from the group consisting of: proliferation in an activated T lymphocyte cell, differentiation in an activated T lymphocyte cell, cytotoxic T cell (CTL) activity, proliferation in an activated B cell, differentiation in an activated B cell, proliferation in a natural killer (NK) cell, differentiation in a NK cell, cytokine secretion by an activated T cell or an NK cell, and NK/lymphocyte activated killer (LAK) anti-tumor cytotoxicity.

Mutant cytokine molecules useful as effector moieties in the multispecific or multifunctional polypeptide can be prepared by deletion, substitution, insertion or modification using genetic or chemical methods well known in the art. Genetic methods may include site-specific mutagenesis of the encoding DNA sequence, PCR, gene synthesis, and the like. The correct nucleotide changes can be verified for example by sequencing. Substitution or insertion may involve natural as well as non-natural amino acid residues. Amino acid modification includes well known methods of chemical modification such as the addition or removal of glycosylation sites or carbohydrate attachments, and the like.

In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is GM-CSF. In a specific embodiment, the GM-CSF cytokine can elicit proliferation and/or differentiation in a granulocyte, a monocyte or a dendritic cell. In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is IFN-α. In a specific embodiment, the IFN-α cytokine can elicit one or more of the cellular responses selected from the group consisting of: inhibiting viral replication in a virus-infected cell, and upregulating the expression of major histocompatibility complex I (MHC I). In another specific embodiment, the IFN-α cytokine can inhibit proliferation in a tumor cell. In one embodiment the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is IFNγ. In a specific embodiment, the IFN-γ cytokine can elicit one or more of the cellular responses selected from the group of: increased macrophage activity, increased expression of MHC molecules, and increased NK cell activity. In one embodiment the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is IL-7. In a specific embodiment, the IL-7 cytokine can elicit proliferation of T and/or B lymphocytes. In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is IL-8. In a specific embodiment, the IL-8 cytokine can elicit chemotaxis in neutrophils. In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide, is MIP-1α. In a specific embodiment, the MIP-1α cytokine can elicit chemotaxis in monocytes and T lymphocyte cells. In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is MIP-1β. In a specific embodiment, the MIP-1β cytokine can elicit chemotaxis in monocytes and T lymphocyte cells. In one embodiment, the cytokine, particularly a single-chain cytokine, of the multispecific or multifunctional polypeptide is TGF-β. In a specific embodiment, the TGF-β cytokine can elicit one or more of the cellular responses selected from the group consisting of: chemotaxis in monocytes, chemotaxis in macrophages, upregulation of IL-1 expression in activated macrophages, and upregulation of IgA expression in activated B cells.

In one embodiment, the multispecific or multifunctional polypeptide of the invention binds to an cytokine receptor with a dissociation constant (K_D) that is at least about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5 or 10 times greater than that for a control cytokine. In another embodiment, the multispecific or multifunctional polypeptide binds to an cytokine receptor with a K_D that is at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 times greater than that for a corresponding multispecific or multifunctional polypeptide comprising two or more effector moieties. In another embodiment, the multispecific or multifunctional polypeptide binds to an cytokine receptor with a dissociation constant K_D that is about 10 times greater than that for a corresponding the multispecific or multifunctional polypeptide comprising two or more cytokines.

In some embodiments, the multispecific molecules disclosed herein include a cytokine molecule. In embodiments, the cytokine molecule includes a full length, a fragment or a variant of a cytokine; a cytokine receptor domain, e.g., a cytokine receptor dimerizing domain; or an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor.

In some embodiments the cytokine molecule is chosen from IL-2, IL-12, IL-15, IL-18, IL-7, IL-21, or interferon gamma, or a fragment or variant thereof, or a combination of any of the aforesaid cytokines. The cytokine molecule can be a monomer or a dimer. In embodiments, the cytokine molecule can further include a cytokine receptor dimerizing domain.

In other embodiments, the cytokine molecule is an agonist of a cytokine receptor, e.g., an antibody molecule (e.g., an agonistic antibody) to a cytokine receptor chosen from an IL-15Ra or IL-21R.

In one embodiment, the cytokine molecule is IL-15, e.g., human IL-15 (e.g., comprising the amino acid sequence: NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLES GDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 2170), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 2170.

In some embodiments, the cytokine molecule comprises a receptor dimerizing domain, e.g., an IL15Ralpha dimerizing domain. In one embodiment, the IL15Ralpha dimerizing domain comprises the amino acid sequence: MAPRRARGCRTLGLPALLLLLLLRPPATRGITCPPPMSVEHADIWVKSYSLYSRERYICN SGFKRKAGTSSLTECVL (SEQ ID NO: 2180), a fragment thereof, or an amino acid

sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 2180. In some embodiments, the cytokine molecule (e.g., IL-15) and the receptor dimerizing domain (e.g., an IL15Ralpha dimerizing domain) of the multispecific molecule are covalently linked, e.g., via a linker (e.g., a Gly-Ser linker, e.g., a linker comprising the amino acid sequence SGGSGGGGSGGGSGGGGSLQ (SEQ ID NO: 2190). In other embodiments, the cytokine molecule (e.g., IL-15) and the receptor dimerizing domain (e.g., an IL15Ralpha dimerizing domain) of the multispecific molecule are not covalently linked, e.g., are non-covalently associated.

In other embodiments, the cytokine molecule is IL-2, e.g., human IL-2 (e.g., comprising the amino acid sequence: APTSSSTKKTQLQLEHLLLDLQMILNGINNYKNPKL-TRMLTFKFYMPKKATELKHLQCL EEELKPLEEVLN-LAQSKNFHLRPRDLISNINVIVLELKGSETTFMCEYA-DETATIVEFLNR WITFCQSIISTLT (SEQ ID NO: 2191), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO:2191).

In other embodiments, the cytokine molecule is IL-18, e.g., human IL-18 (e.g., comprising the amino acid sequence: YFGKLESKLSVIRNLNDQVLFIDQGNR-PLFEDMTDSDCRDNAPRTIFIISMYKDSQPRGM AVTISVKCEKISTLSCENKIISFKEMNPPDNIKDTKS-DIIFFQRSVPGHDNKMQFESSSYEG YFLACEKER-DLFKLILKKEDELGDRSIMFTVQNED (SEQ ID NO: 2192), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 2192).

In other embodiments, the cytokine molecule is IL-21, e.g., human IL-21 (e.g., comprising the amino acid sequence: QGQDRHMIRMRQLIDI-VDQLKNYVNDLVPEFLPAPEDVETNCEWS-AFSCFQKAQLKSA NTGNNERIINVSIKKLKRKPPST-NAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMI HQHLSSRTHGSEDS (SEQ ID NO: 2193), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 2193).

In yet other embodiments, the cytokine molecule is interferon gamma, e.g., human interferon gamma (e.g., comprising the amino acid sequence: QDPYVKEAE-NLKKYFNAGHSDVADNGTLFLGILKNWKEESDRKIM QSQIVSFYFKLFK NFKDDQSIQKSVE-TIKEDMNVKFFNSNKKKRDDFEKLT-NYSVTDLNVQRKAIHELIQVM AELSPAAKTGKRKR-SQMLFRG (SEQ ID NO: 2194), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 2194).

Immune Cell Engagers

The immune cell engagers, e.g., first and/or second immune cell engager, of the multispecific or multifunctional molecules disclosed herein can mediate binding to, and/or activation of, an immune cell, e.g., an immune effector cell. In some embodiments, the immune cell is chosen from a T cell, an NK cell, a B cell, a dendritic cell, or a macrophage cell engager, or a combination thereof. In some embodiments, the immune cell engager is chosen from one, two, three, or all of a T cell engager, NK cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager, or a combination thereof. The immune cell engager can be an agonist of the immune system. In some embodiments, the immune cell engager can be an antibody molecule, a ligand molecule (e.g., a ligand that further comprises an immunoglobulin constant region, e.g., an Fc region), a small molecule, a nucleotide molecule.

Natural Killer Cell Engagers

Natural Killer (NK) cells recognize and destroy tumors and virus-infected cells in an antibody-independent manner. The regulation of NK cells is mediated by activating and inhibiting receptors on the NK cell surface. One family of activating receptors is the natural cytotoxicity receptors (NCRs) which include NKp30, NKp44 and NKp46. The NCRs initiate tumor targeting by recognition of heparan sulfate on cancer cells. NKG2D is a receptor that provides both stimulatory and costimulatory innate immune responses on activated killer (NK) cells, leading to cytotoxic activity. DNAM1 is a receptor involved in intercellular adhesion, lymphocyte signaling, cytotoxicity and lymphokine secretion mediated by cytotoxic T-lymphocyte (CTL) and NK cell. DAP10 (also known as HCST) is a transmembrane adapter protein which associates with KLRK1 to form an activation receptor KLRK1-HCST in lymphoid and myeloid cells; this receptor plays a major role in triggering cytotoxicity against target cells expressing cell surface ligands such as WIC class I chain-related MICA and MICB, and U(optionally L1)6-binding proteins (ULBPs); it KLRK1-HCST receptor plays a role in immune surveillance against tumors and is required for cytolysis of tumors cells; indeed, melanoma cells that do not express KLRK1 ligands escape from immune surveillance mediated by NK cells. CD16 is a receptor for the Fc region of IgG, which binds complexed or aggregated IgG and also monomeric IgG and thereby mediates antibody-dependent cellular cytotoxicity (ADCC) and other antibody-dependent responses, such as phagocytosis.

In some embodiments, the NK cell engager is a viral hemagglutinin (HA), HA is a glycoprotein found on the surface of influenza viruses. It is responsible for binding the virus to cells with sialic acid on the membranes, such as cells in the upper respiratory tract or erythrocytes. HA has at least 18 different antigens. These subtypes are named H1 through H18. NCRs can recognize viral proteins. NKp46 has been shown to be able to interact with the HA of influenza and the HA-NA of Paramyxovirus, including Sendai virus and Newcastle disease virus. Besides NKp46, NKp44 can also functionally interact with HA of different influenza subtypes.

The present disclosure provides, inter alia, multispecific (e.g., bi-, tri-, quad-specific) or multifunctional molecules, that are engineered to contain one or more NK cell engagers that mediate binding to and/or activation of an NK cell. Accordingly, in some embodiments, the NK cell engager is selected from an antigen binding domain or ligand that binds to (e.g., activates): NKp30, NKp40, NKp44, NKp46, NKG2D, DNAM1, DAP10, CD16 (e.g., CD16a, CD16b, or

both), CRTAM, CD27, PSGL1, CD96, CD100 (SEMA4D), NKp80, CD244 (also known as SLAMF4 or 2B4), SLAMF6, SLAMF7, KIR2DS2, KIR2DS4, KIR3DS1, KIR2DS3, KIR2DS5, KIR2DS1, CD94, NKG2C, NKG2E, or CD160.

In one embodiment, the NK cell engager is a ligand of NKp30 is a B7-6, e.g., comprises the amino acid sequence of: DLKVEMMAGGTQITPLNDNVTIFCNIFYSQPLNITSMGITWFWKSLTFDKEVKVFEFFGD HQEAFRPGAIVSPWRLKSGDASLRLPGIQLEEAGEYRCEVVVTPLKAQGTVQLEVVASP ASRLLLDQVGMKENEDKYMCESSGFYPEAINITWEKQTQKFPHPIEISEDVITGPTIKNM DGTFNVTSCLKLNSSQEDPGTVYQCVVRHASLHTPLRSNFTLTAARHSLSETEKTDNFS (SEQ ID NO: 3291), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3291.

In other embodiments, the NK cell engager is a ligand of NKp44 or NKp46, which is a viral HA. Viral hemagglutinins (HA) are glyco proteins which are on the surface of viruses. HA proteins allow viruses to bind to the membrane of cells via sialic acid sugar moieties which contributes to the fusion of viral membranes with the cell membranes (see e.g., Eur J Immunol. 2001 September; 31(9):2680-9 "Recognition of viral hemagglutinins by NKp44 but not by NKp30"; and Nature. 2001 Feb. 22; 409(6823):1055-60 "Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells" the contents of each of which are incorporated by reference herein).

In other embodiments, the NK cell engager is a ligand of NKG2D chosen from MICA, MICB, or ULBP1, e.g., wherein:

(i) MICA comprises the amino acid sequence: EPHSLRYNLTVLSWDGSVQSGFLTEVHLDGQPFLRCDRQKCRAKPQGQWAEDVLGNK TWDRETRDLTGNGKDLRMTLAHIKDQKEGLHSLQEIRVCEIHEDNSTRS SQHFYYDGEL FLSQNLETKEWTMPQSSRAQTLAMNVRNFLKEDAMKTKTHYHAMHADCLQELRRYLK SGVVLRRTVPPMVNVTRSEASEGNITVTCRASGFYPWNITLSWRQDGVSLSHDTQQWG DVLPDGNGTYQTWVATRICQGEEQRFTCYMEHSGNHSTHPVPSGKVLVLQSHW (SEQ ID NO: 3292), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3292;

(ii) MICB comprises the amino acid sequence: AEPHSLRYNLMVLSQDESVQSGFLAEGHLDGQPFLRYDRQKRRAKPQGQWAEDVLGA KTWDTETEDLTENGQDLRRTLTHIKDQKGGLHSLQEIRVCEIHEDS STRGSRHFYYDGEL FLSQNLETQESTVPQSSRAQTLAMNVTNFWKEDAMKTKTHYRAMQADCLQKLQRYLK SGVAIRRTVPPMVNVTCSEVSEGNITVTCRASSFYPRNITLTWRQDGVSLSHNTQQWGD VLPDGNGTYQTWVATRIRQGEEQRFTCYMEHSGNHGTHPVPSGKVLVLQSQRTD (SEQ ID NO: 3293), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3293; or

(iii) ULBP1 comprises the amino acid sequence: GWVDTHCLCYDFIITPKSRPEPQWCEVQGLVDERPFLHYDCVNHKAKAFASLGKKVNV TKTWEEQTETLRDVVDFLKGQLLDIQVENLIPIEPLTLQARMSCEHEAHGHGRGSWQFL FNGQKFLLFDSNNRKWTALHPGAKKMTEKWEKNRDVTMFFQKISLGDCKMWLEEFL MYWEQMLDPTKPPSLAPG (SEQ ID NO: 3294), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3294.

In other embodiments, the NK cell engager is a ligand of DNAM1 chosen from NECTIN2 or NECL5, e.g., wherein:

(i) NECTIN2 comprises the amino acid sequence: QDVRVQVLPEVRGQLGGTVELPCHLLPPVPGLYISLVTWQRPDAPANHQNVAAFHPKM GPSFPSPKPGSERLSFVSAKQSTGQDTEAELQDATLALHGLTVEDEGNYTCEFATFPKGS VRGMTWLRVIAKPKNQAEAQKVTFSQDPTTVALCISKEGRPPARISWLSSLDWEAKETQ VSGTLAGTVTVTSRFTLVPSGRADGVTVTCKVEHESF EEPALIPVTLSVRYPPEVSISGYD DNWYLGRTDATLSCDVRSNPEPTGYDWSTTSGTFPTSAVAQGSQLVIHAVDSLFNTTFV CTVTNAVGMGRAEQVIFVRETPNTAGAGATGG (SEQ ID NO: 3295), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3295; or

(ii) NECL5 comprises the amino acid sequence: WPPPGTGDVVVQAPTQVPGFLGDSVTLPCYLQVPNMEVTHVSQLTWARHGESGSMAV FHQTQGPSYSESKRLEFVAARLGAELRNASLRMFGLRVEDEGNYTCLFVTFPQGSRSVD IWLRVLAKPQNTAEVQKVQLTGEPVPMARCVSTGGRPPAQITWHSDLGGMPNTSQVPG FLSGTVTVTSLWILVPSSQVDGKNVTCKVEHESFEKPQLLTVNLTVYYPPEVSISGYDNN WYLGQNEATLTCDARSNPEPTGYNWSTTMGPLPPFAVAQGAQLLIRPVDKPINTTLICN VTNALGARQAELTVQVKEGPPSEHSGISRN (SEQ ID NO: 3296), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3296.

In yet other embodiments, the NK cell engager is a ligand of DAP10, which is an adapter for NKG2D (see e.g., Proc Natl Acad Sci USA. 2005 May 24; 102(21): 7641-7646; and Blood, 15 Sep. 2011 Volume 118, Number 11, the full contents of each of which is incorporated by reference herein).

In other embodiments, the NK cell engager is a ligand of CD16, which is a CD16a/b ligand, e.g., a CD16a/b ligand further comprising an antibody Fc region (see e.g., Front Immunol. 2013; 4: 76 discusses how antibodies use the Fc to trigger NK cells through CD16, the full contents of which are incorporated herein).

In other embodiments, the NK cell engager is a ligand of CRTAM, which is NECL2, e.g., wherein NECL2 comprises the amino acid sequence: QNLFTKDVTVIEGEVATISCQVNKSDDSVIQLLNPNRQTIYFRDFRPLKDSRFQLLNFSSS ELKVSLTNVSISDEGRYFCQLYTDPPQESYTTITVLVPPRNLMIDIQKDTAVEGEEIEVNC TAMASKPATTIRWFKGNTELKGKSEVEEWSDMYTVTSQLMLKVHKEDDGVPVICQVEHPAVTGNLQTQRYLEVQYKPQVHIQMTYPLQGLTREGDALELTCEAIGKPQPVMVTWV RVDDEMPQHAVLSGPNLFINNLNKTDNGTYRCEASNIVGKAHSDYMLYVYDPPTTIPPP TTTTTTTTTTTTTILTIITDSRAGEEGSIRAVDH (SEQ ID NO: 3297), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3297.

In other embodiments, the NK cell engager is a ligand of CD27, which is CD70, e.g., wherein CD70 comprises the amino acid sequence: QRFAQAQQQLPLESLGWDVAELQLNHTGPQQDPRLYWQGGPALGRSFLHGPELDKGQ LRIHRDGIYMVHIQVTLAICSSTTASRHHPTTLAVGICSPASRSISLLRLSFHQGCTIASQR LTPLARGDTLCTNLTGTLLPSRNTDETFFGVQWVRP (SEQ ID NO: 3298), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3298.

In other embodiments, the NK cell engager is a ligand of PSGL1, which is L-selectin (CD62L), e.g., wherein L-selectin comprises the amino acid sequence: WTYHYSEKPMNWQRARRFCRDNYTDLVAIQNKAEIEYLEKTLPFSRSYYWIGIRKIGGI WTWVGTNKSLTEEAENWGDGEPNNKKNKEDCVEIYIKRNKDAGKWNDDACHKLKAA LCYTASCQPWSCSGHGECVEIINNYTCNCDVGYYGPQCQFVIQCEPLEAPELGTMDCTH PLGNFSFSSQCAFSCSEGTNLTGIEETTCGPFGNWSSPEPTCQVIQCEPLSAPDLGIMNCSH PLASFSFTSACTFICSEGTELIGKKKTICESSGIWSNPSPICQKLDKSFSMIKEGDYN (SEQ ID NO: 3299), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3299.

In other embodiments, the NK cell engager is a ligand of CD96, which is NECL5, e.g., wherein NECL5 comprises the amino acid sequence: WPPPGTGDVVVQAPTQVPGFLGDSVTLPCYLQVPNMEVTHVSQLTWARHGESGSMAV FHQTQGPSYSESKRLEFVAARLGAELRNASLRMFGLRVEDEGNYTCLFVTFPQGSRSVD IWLRVLAKPQNTAEVQKVQLTGEPVPMARCVSTGGRPPAQITWHSDLGGMPNTSQVPG FLSGTVTVTSLWILVPSSQVDGKNVTCKVEHESFEKPQLLTVNLTVYYPPEVSISGYDNN WYLGQNEATLTCDARSNPEPTGYNWSTTMGPLPPFAVAQGAQLLIRPVDKPINTTLICN VTNALGARQAELTVQVKEGPPSEHSGISRN (SEQ ID NO: 3296), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3296.

In other embodiments, the NK cell engager is a ligand of CD100 (SEMA4D), which is CD72, e.g., wherein CD72 comprises the amino acid sequence: RYLQVSQQLQQTNRVLEVTNSSLRQQLRLKITQLGQSAEDLQGSRRELAQSQEALQVEQ RAHQAAEGQLQACQADRQKTKETLQSEEQQRRALEQKLSNMENRLKPFFTCGSADTCC PSGWIMHQKSCFYISLTSKNWQESQKQCETLSSKLATFSEIYPQSHSYYFLNSLLPNGGS GNSYWTGLSSNKDWKLTDDTQRTRTYAQSSKCNKVHKTWSWWTLESESCRSSLPYICE MTAFRFPD (SEQ ID NO: 3300), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3300.

In other embodiments, the NK cell engager is a ligand of NKp80, which is CLEC2B (AICL), e.g., wherein CLEC2B (AICL) comprises the amino acid sequence: KLTRDSQSLCPYDWIGFQNKCYYFSKEEGDWNSSKYNCSTQHADLTIIDNIEEMNFLRR YKCSSDHWIGLKMAKNRTGQWVDGATFTKSFGMRGSEGCAYLSDDGAATARCYTER KWICRKRIH (SEQ ID NO: 3301), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3301.

In other embodiments, the NK cell engager is a ligand of CD244, which is CD48, e.g., wherein CD48 comprises the amino acid sequence: QGHLVHMTVVSGSNVTLNISESLPENYKQLTWFYTFDQKIVEWDSRKSKYFESKFKGR VRLDPQSGALYISKVQKEDNSTYIMRVLKKTGNEQEWKIKLQVLDPVPKPVIKIEKIEDM DDNCYLKLSCVIPGESVNYTWYGDKRPFPKELQNSVLETTLMPHNYSRCYTCQVSNSVS SKNGTVCLSPPCTLARS (SEQ ID NO: 3302), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3302.

T Cell Engagers

The present disclosure provides, inter alia, multispecific (e.g., bi-, tri-, quad-specific) or multifunctional molecules, that are engineered to contain one or more T cell engager that mediate binding to and/or activation of a T cell. In some embodiments, the T cell engager is an antigen binding domain that binds to, e.g., activates TCRβ, e.g., a TCRβV region, as described herein. In some embodiments, the T cell engager is selected from an antigen binding domain or

ligand that binds to (e.g., and in some embodiments activates) one or more of CD3, TCRα, TCRγ, TCRζ, ICOS, CD28, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, SLAM, CD2, or CD226. In other embodiments, the T cell engager is selected from an antigen binding domain or ligand that binds to and does not activate one or more of CD3, TCRα, TCRγ, TCRζ, ICOS, CD28, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, SLAM, CD2, or CD226.

B Cell, Macrophage & Dendritic Cell Engagers

Broadly, B cells, also known as B lymphocytes, are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines. Macrophages are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, cancer cells via phagocytosis. Besides phagocytosis, they play important roles in nonspecific defense (innate immunity) and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. For example, they are important as antigen presenters to T cells. Beyond increasing inflammation and stimulating the immune system, macrophages also play an important anti-inflammatory role and can decrease immune reactions through the release of cytokines. Dendritic cells (DCs) are antigen-presenting cells that function in processing antigen material and present it on the cell surface to the T cells of the immune system.

The present disclosure provides, inter alia, multispecific (e.g., bi-, tri-, quad-specific) or multifunctional molecules, that include, e.g., are engineered to contain, one or more B cell, macrophage, and/or dendritic cell engager that mediate binding to and/or activation of a B cell, macrophage, and/or dendritic cell.

Accordingly, in some embodiments, the immune cell engager comprises a B cell, macrophage, and/or dendritic cell engager chosen from one or more of CD40 ligand (CD40L) or a CD70 ligand; an antibody molecule that binds to CD40 or CD70; an antibody molecule to OX40; an OX40 ligand (OX40L); an agonist of a Toll-like receptor (e.g., as described herein, e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4), or a TLR9 agonists); a 41BB; a CD2; a CD47; or a STING agonist, or a combination thereof.

In some embodiments, the B cell engager is a CD40L, an OX40L, or a CD70 ligand, or an antibody molecule that binds to OX40, CD40 or CD70.

In some embodiments, the macrophage engager is a CD2 agonist. In some embodiments, the macrophage engager is an antigen binding domain that binds to: CD40L or antigen binding domain or ligand that binds CD40, a Toll like receptor (TLR) agonist (e.g., as described herein), e.g., a TLR9 or TLR4 (e.g., caTLR4 (constitutively active TLR4), CD47, or a STING agonist. In some embodiments, the STING agonist is a cyclic dinucleotide, e.g., cyclic di-GMP (cdGMP) or cyclic di-AMP (cdAMP). In some embodiments, the STING agonist is biotinylated.

In some embodiments, the dendritic cell engager is a CD2 agonist. In some embodiments, the dendritic cell engager is a ligand, a receptor agonist, or an antibody molecule that binds to one or more of: OX40L, 41BB, a TLR agonist (e.g., as described herein) (e.g., TLR9 agonist, TLR4 (e.g., caTLR4 (constitutively active TLR4)), CD47, or and a STING agonist. In some embodiments, the STING agonist is a cyclic dinucleotide, e.g., cyclic di-GMP (cdGMP) or cyclic di-AMP (cdAMP). In some embodiments, the STING agonist is biotinylated.

In other embodiments, the immune cell engager mediates binding to, or activation of, one or more of a B cell, a macrophage, and/or a dendritic cell. Exemplary B cell, macrophage, and/or dendritic cell engagers can be chosen from one or more of CD40 ligand (CD40L) or a CD70 ligand; an antibody molecule that binds to CD40 or CD70; an antibody molecule to OX40; an OX40 ligand (OX40L); a Toll-like receptor agonist (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4) or a TLR9 agonist); a 41BB agonist; a CD2; a CD47; or a STING agonist, or a combination thereof.

In some embodiments, the B cell engager is chosen from one or more of a CD40L, an OX40L, or a CD70 ligand, or an antibody molecule that binds to OX40, CD40 or CD70.

In other embodiments, the macrophage cell engager is chosen from one or more of a CD2 agonist; a CD40L; an OX40L; an antibody molecule that binds to OX40, CD40 or CD70; a Toll-like receptor agonist or a fragment thereof (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4)); a CD47 agonist; or a STING agonist.

In other embodiments, the dendritic cell engager is chosen from one or more of a CD2 agonist, an OX40 antibody, an OX40L, 41BB agonist, a Toll-like receptor agonist or a fragment thereof (e.g., a TLR4, e.g., a constitutively active TLR4 (caTLR4)), CD47 agonist, or a STING agonist.

In one embodiment, the OX40L comprises the amino acid sequence: QVSHRYPRIQSIKVQFTEYKKEKGFILTSQKEDEIMKVQNNSVIINCDGFYLISLKGYFSQ EVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKDKVYLNVTTDNTSL DDFHVNGGE LILIHQNPGEFCVL (SEQ ID NO: 3303), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3303.

In another embodiment, the CD40L comprises the amino acid sequence: MQKGDQNPQIAAHVISEASSKTTSVLQWAEKGYYTMSNNLVTLENGKQLTVKRQGLY YIYAQVTFCSNREASSQAPFIASLCLKSPGRFERILLRAANTHSSAKPCGQQSIHLG GVFE LQPGASVFVNVTDPSQVSHGTGFTSFGLLKL (SEQ ID NO: 3304), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3304.

In yet other embodiments, the STING agonist comprises a cyclic dinucleotide, e.g., a cyclic di-GMP (cdGMP), a cyclic di-AMP (cdAMP), or a combination thereof, optionally with 2',5' or 3',5' phosphate linkages.

In one embodiment, the immune cell engager includes 41BB ligand, e.g., comprising the amino acid sequence: ACPWAVSGARASPGSAASPRLREGPELSPDDPAGLLDLRQGMFAQLVAQNVLLIDGPLS WYSDPGLAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLELRRVVAGEGSGSVSLALH LQPLRSAAGAAALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHLHTEARARH AWQLTQGATVLGLFRVTPEIPAGLPSPRSE (SEQ ID NO: 3305), a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical

thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3305.

Toll-Like Receptors

Toll-Like Receptors (TLRs) are evolutionarily conserved receptors are homologues of the *Drosophila* Toll protein, and recognize highly conserved structural motifs known as pathogen-associated microbial patterns (PAMPs), which are exclusively expressed by microbial pathogens, or danger-associated molecular patterns (DAMPs) that are endogenous molecules released from necrotic or dying cells. PAMPs include various bacterial cell wall components such as lipopolysaccharide (LPS), peptidoglycan (PGN) and lipopeptides, as well as flagellin, bacterial DNA and viral double-stranded RNA. DAMPs include intracellular proteins such as heat shock proteins as well as protein fragments from the extracellular matrix. Stimulation of TLRs by the corresponding PAMPs or DAMPs initiates signaling cascades leading to the activation of transcription factors, such as AP-1, NF-κB and interferon regulatory factors (IRFs). Signaling by TLRs results in a variety of cellular responses, including the production of interferons (IFNs), pro-inflammatory cytokines and effector cytokines that direct the adaptive immune response. TLRs are implicated in a number of inflammatory and immune disorders and play a role in cancer (Rakoff-Nahoum S. & Medzhitov R., 2009. Toll-like receptors and cancer. Nat Revs Cancer 9:57-63.)

TLRs are type I transmembrane proteins characterized by an extracellular domain containing leucine-rich repeats (LRRs) and a cytoplasmic tail that contains a conserved region called the Toll/IL-1 receptor (TIR) domain. Ten human and twelve murine TLRs have been characterized, TLR1 to TLR10 in humans, and TLR1 to TLR9, TLR11, TLR12 and TLR13 in mice, the homolog of TLR10 being a pseudogene. TLR2 is essential for the recognition of a variety of PAMPs from Gram-positive bacteria, including bacterial lipoproteins, lipomannans and lipoteichoic acids. TLR3 is implicated in virus-derived double-stranded RNA. TLR4 is predominantly activated by lipopolysaccharide. TLR5 detects bacterial flagellin and TLR9 is required for response to unmethylated CpG DNA. Finally, TLR7 and TLR8 recognize small synthetic antiviral molecules, and single-stranded RNA was reported to be their natural ligand. TLR11 has been reported to recognize uropathogenic *E. coli* and a profilin-like protein from *Toxoplasma gondii*. The repertoire of specificities of the TLRs is apparently extended by the ability of TLRs to heterodimerize with one another. For example, dimers of TLR2 and TLR6 are required for responses to diacylated lipoproteins while TLR2 and TLR1 interact to recognize triacylated lipoproteins. Specificities of the TLRs are also influenced by various adapter and accessory molecules, such as MD-2 and CD14 that form a complex with TLR4 in response to LPS.

TLR signaling consists of at least two distinct pathways: a MyD88-dependent pathway that leads to the production of inflammatory cytokines, and a MyD88-independent pathway associated with the stimulation of IFN-β and the maturation of dendritic cells. The MyD88-dependent pathway is common to all TLRs, except TLR3 (Adachi O. et al., 1998. Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. Immunity. 9(1):143-50). Upon activation by PAMPs or DAMPs, TLRs hetero- or homodimerize inducing the recruitment of adaptor proteins via the cytoplasmic TIR domain. Individual TLRs induce different signaling responses by usage of the different adaptor molecules. TLR4 and TLR2 signaling requires the adaptor TIRAP/Mal, which is involved in the MyD88-dependent pathway. TLR3 triggers the production of IFN-β in response to double-stranded RNA, in a MyD88-independent manner, through the adaptor TRIF/TICAM-1. TRAM/TICAM-2 is another adaptor molecule involved in the MyD88-independent pathway which function is restricted to the TLR4 pathway.

TLR3, TLR7, TLR8 and TLR9 recognize viral nucleic acids and induce type I IFNs. The signaling mechanisms leading to the induction of type I IFNs differ depending on the TLR activated. They involve the interferon regulatory factors, IRFs, a family of transcription factors known to play a critical role in antiviral defense, cell growth and immune regulation. Three IRFs (IRF3, IRF5 and IRF7) function as direct transducers of virus-mediated TLR signaling. TLR3 and TLR4 activate IRF3 and IRF7, while TLR7 and TLR8 activate IRF5 and IRF7 (Doyle S. et al., 2002. IRF3 mediates a TLR3/TLR4-specific antiviral gene program. Immunity. 17(3):251-63). Furthermore, type I IFN production stimulated by TLR9 ligand CpG-A has been shown to be mediated by PI(3)K and mTOR (Costa-Mattioli M. & Sonenberg N. 2008. RAPping production of type I interferon in pDCs through mTOR. Nature Immunol. 9: 1097-1099).

TLR-9

TLR9 recognizes unmethylated CpG sequences in DNA molecules. CpG sites are relatively rare (~1%) on vertebrate genomes in comparison to bacterial genomes or viral DNA. TLR9 is expressed by numerous cells of the immune system such as B lymphocytes, monocytes, natural killer (NK) cells, and plasmacytoid dendritic cells. TLR9 is expressed intracellularly, within the endosomal compartments and functions to alert the immune system of viral and bacterial infections by binding to DNA rich in CpG motifs. TLR9 signals leads to activation of the cells initiating pro-inflammatory reactions that result in the production of cytokines such as type-I interferon and IL-12.

TLR Agonists

A TLR agonist can agonize one or more TLR, e.g., one or more of human TLR-1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In some embodiments, an adjunctive agent described herein is a TLR agonist. In some embodiments, the TLR agonist specifically agonizes human TLR-9. In some embodiments, the TLR-9 agonist is a CpG moiety. As used herein, a CpG moiety, is a linear dinucleotide having the sequence: 5'-C-phosphate-G-3', that is, cytosine and guanine separated by only one phosphate.

In some embodiments, the CpG moiety comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more CpG dinucleotides. In some embodiments, the CpG moiety consists of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 CpG dinucleotides. In some embodiments, the CpG moiety has 1-5, 1-10, 1-20, 1-30, 1-40, 1-50, 5-10, 5-20, 5-30, 10-20, 10-30, 10-40, or 10-50 CpG dinucleotides.

In some embodiments, the TLR-9 agonist is a synthetic ODN (oligodeoxynucleotides). CpG ODNs are short synthetic single-stranded DNA molecules containing unmethylated CpG dinucleotides in particular sequence contexts (CpG motifs). CpG ODNs possess a partially or completely phosphorothioated (PS) backbone, as opposed to the natural phosphodiester (PO) backbone found in genomic bacterial DNA. There are three major classes of CpG ODNs: classes A, B and C, which differ in their immunostimulatory activities. CpG-A ODNs are characterized by a PO central CpG-containing palindromic motif and a PS-modified 3' poly-G string. They induce high IFN-α production from pDCs but

are weak stimulators of TLR9-dependent NF-κB signaling and pro-inflammatory cytokine (e.g. IL-6) production. CpG-B ODNs contain a full PS backbone with one or more CpG dinucleotides. They strongly activate B cells and TLR9-dependent NF-κB signaling but weakly stimulate IFN-α secretion. CpG-C ODNs combine features of both classes A and B. They contain a complete PS backbone and a CpG-containing palindromic motif. C-Class CpG ODNs induce strong IFN-α production from pDC as well as B cell stimulation.

Tumor-Targeting Moieties

The present disclosure provides, inter alia, multispecific (e.g., bi-, tri-, tetra-specific) molecules, that include, e.g., are engineered to contain, one or more tumor specific targeting moieties that direct the molecule to a tumor cell.

In certain embodiments, the multispecific molecules disclosed herein include a tumor-targeting moiety. The tumor targeting moiety can be chosen from an antibody molecule (e.g., an antigen binding domain as described herein), a receptor or a receptor fragment, or a ligand or a ligand fragment, or a combination thereof. In some embodiments, the tumor targeting moiety associates with, e.g., binds to, a tumor cell (e.g., a molecule, e.g., antigen, present on the surface of the tumor cell). In certain embodiments, the tumor targeting moiety targets, e.g., directs the multispecific molecules disclosed herein to a cancer (e.g., a cancer or tumor cells). In some embodiments, the cancer is chosen from a hematological cancer, a solid cancer, a metastatic cancer, or a combination thereof.

In some embodiments, the multispecific molecule, e.g., the tumor-targeting moiety, binds to a solid tumor antigen or a stromal antigen. The solid tumor antigen or stromal antigen can be present on a solid tumor, or a metastatic lesion thereof. In some embodiments, the solid tumor is chosen from one or more of pancreatic (e.g., pancreatic adenocarcinoma), breast, colorectal, lung (e.g., small or non-small cell lung cancer), skin, ovarian, or liver cancer. In one embodiment, the solid tumor is a fibrotic or desmoplastic solid tumor. For example, the solid tumor antigen or stromal antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium.

In certain embodiments, the solid tumor antigen is chosen from one or more of: PDL1, CD47, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PMSA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, MC1R, catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, MUC-1, CA-125, BAGE, GAGE, NY-ESO-1, 13-catenin, CDK4, CDC27, CD47, a actinin-4, TRP1/gp75, TRP2, gp100, Melan-A/MART1, gangliosides, WT1, EphA3, Epidermal growth factor receptor (EGFR), MART-2, MART-1, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RUI1, RUI2, SAGE, TRG, TRP1, TSTA, Folate receptor alpha, L1-CAM, CAIX, EGFRvIII, gpA33, GD3, GM2, VEGFR, Intergrins (Integrin alphaVbeta3, Integrin alpha5Beta1), Carbohydrates (Le), IGF1R, EPHA3, TRAILR1, TRAILR2, or RANKL.

In other embodiments, the multispecific molecule, e.g., the tumor-targeting moiety, binds to a molecule, e.g., antigen, present on the surface of a hematological cancer, e.g., a leukemia or a lymphoma. In some embodiments, the hematological cancer is a B-cell or T cell malignancy. In some embodiments, the hematological cancer is chosen from one or more of a Hodgkin's lymphoma, Non-Hodgkin's lymphoma (e.g., B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome (MDS), multiple myeloma, or acute lymphocytic leukemia. In embodiments, the cancer is other than acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS). In embodiments, the hematological antigen is chosen from CD47, CD99, CD30, CD38, SLAMF7, or NY-ESO1. In some embodiments, the hematological antigen is chosen from is chosen from one or more of: BCMA, CD19, CD20, CD22, CD33, CD123, FcRH5, CLEC12, or CD179A.

Stromal Modifying Moieties

Solid tumors have a distinct structure that mimics that of normal tissues and comprises two distinct but interdependent compartments: the parenchyma (neoplastic cells) and the stroma that the neoplastic cells induce and in which they are dispersed. All tumors have stroma and require stroma for nutritional support and for the removal of waste products. In the case of tumors which grow as cell suspensions (e.g., leukemias, ascites tumors), the blood plasma serves as stroma (Connolly J L et al. Tumor Structure and Tumor Stroma Generation. In: Kufe D W et al., editors. Holland-Frei *Cancer Medicine*. 6th edition. Hamilton: BC Decker; 2003). The stroma includes a variety of cell types, including fibroblasts/myofibroblasts, glial, epithelial, fat, vascular, smooth muscle, and immune cells along with extracellular matrix (ECM) and extracellular molecules (Li Hanchen et al. Tumor Microenvironment: The Role of the Tumor Stroma in Cancer. *J of Cellular Biochemistry* 101: 805-815 (2007)).

Stromal modifying moieties described herein include moieties (e.g., proteins, e.g., enzymes) capable of degrading a component of the stroma, e.g., an ECM component, e.g., a glycosaminoglycan, e.g., hyaluronan (also known as hyaluronic acid or HA), chondroitin sulfate, chondroitin, dermatan sulfate, heparin sulfate, heparin, entactin, tenascin, aggrecan and keratin sulfate; or an extracellular protein, e.g., collagen, laminin, elastin, fibrinogen, fibronectin, and vitronectin.

Stromal Modifying Enzymes

In some embodiments, the stromal modifying moiety is an enzyme. For example, the stromal modifying moiety can include, but is not limited to a hyaluronidase, a collagenase, a chondroitinase, a matrix metalloproteinase (e.g., macrophage metalloelastase).

Hyaluronidases

Hyaluronidases are a group of neutral- and acid-active enzymes found throughout the animal kingdom. Hyaluronidases vary with respect to substrate specificity, and mechanism of action. There are three general classes of hyaluronidases: (1) Mammalian-type hyaluronidases, (EC 3.2.1.35) which are endo-beta-N-acetylhexosaminidases with tetrasaccharides and hexasaccharides as the major end products. They have both hydrolytic and transglycosidase activities, and can degrade hyaluronan and chondroitin sulfates; (2) Bacterial hyaluronidases (EC 4.2.99.1) degrade hyaluronan and, and to various extents, chondroitin sulfate and dermatan sulfate. They are endo-beta-N-acetylhexosaminidases that operate by a beta elimination reaction that yields primarily disaccharide end products; (3) Hyaluronidases (EC 3.2.1.36)

from leeches, other parasites, and crustaceans are endo-beta-glucuronidases that generate tetrasaccharide and hexasaccharide end products through hydrolysis of the beta 1-3 linkage.

Mammalian hyaluronidases can be further divided into two groups: (1) neutral active and (2) acid active enzymes. There are six hyaluronidase-like genes in the human genome, HYAL1, HYAL2, HYAL3 HYAL4 HYALP1 and PH20/SPAM1. HYALP1 is a pseudogene, and HYAL3 has not been shown to possess enzyme activity toward any known substrates. HYAL4 is a chondroitinase and lacks activity towards hyaluronan. HYAL1 is the prototypical acid-active enzyme and PH20 is the prototypical neutral-active enzyme. Acid active hyaluronidases, such as HYAL1 and HYAL2 lack catalytic activity at neutral pH. For example, HYAL1 has no catalytic activity in vitro over pH 4.5 (Frost and Stern, "A Microtiter-Based Assay for Hyaluronidase Activity Not Requiring Specialized Reagents", Analytical Biochemistry, vol. 251, pp. 263-269 (1997). HYAL2 is an acid active enzyme with a very low specific activity in vitro.

In some embodiments the hyaluronidase is a mammalian hyaluronidase. In some embodiments the hyaluronidase is a recombinant human hyaluronidase. In some embodiments, the hyaluronidase is a neutral active hyaluronidase. In some embodiments, the hyaluronidase is a neutral active soluble hyaluronidase. In some embodiments, the hyaluronidase is a recombinant PH20 neutral-active enzyme. In some embodiments, the hyaluronidase is a recombinant PH20 neutral-active soluble enzyme. In some embodiments the hyaluronidase is glycosylated. In some embodiments, the hyaluronidase possesses at least one N-linked glycan. A recombinant hyaluronidase can be produced using conventional methods known to those of skill in the art, e.g., U.S. Pat. No. 7,767,429, the entire contents of which are incorporated by reference herein.

In some embodiments the hyaluronidase is rHuPH20 (also referred to as Hylenex®; presently manufactured by Halozyme; approved by the FDA in 2005 (see e.g., Scodeller P (2014) Hyaluronidase and other Extracellular Matrix Degrading Enzymes for Cancer Therapy: New Uses and Nano-Formulations. J Carcinog Mutage 5:178; U.S. Pat. Nos. 7,767,429; 8,202,517; 7,431,380; 8,450,470; 8,772,246; 8,580,252, the entire contents of each of which is incorporated by reference herein). rHuPH20 is produced by genetically engineered CHO cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase PH20. In some embodiments the hyaluronidase is glycosylated. In some embodiments, the hyaluronidase possesses at least one N-linked glycan. A recombinant hyaluronidase can be produced using conventional methods known to those of skill in the art, e.g., U.S. Pat. No. 7,767,429, the entire contents of which are incorporated by reference herein. In some embodiments, rHuPH20 has a sequence at least 95% (e.g., at least 96%, 97%, 98%, 99%, 100%) identical to the amino acid sequence of LNFRAPPVIPNVPFLWAWNAPSEFCLGKFDE-PLDMSLFSFIGSPRINATGQGVTIFYVDRL GYY-PYIDSITGVTVNGGIPQKIS-LQDHLDKAKKDITFYMPVDNLGMAVIDWEEWRPTW ARNWKPKDVYKNRSIELVQQQNVQLSL-TEATEKAKQEFEKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKKPGYNGSCFN-VEIKRNDDLSWLWNESTALYPSIYLNTQQS PVAAT-LYVRNRVREAIRVSKIPDAKSPLPVFAY-TRIVFTDQVLKFLSQDELVYTFGETVA LGASGIVIWGTLSIMRSMKSCLLLDNYMETILNPYI-INVTLAAKMCSQVLCQEQGVCIRK NWNSSDYLHLNPDNFAIQLEKGGKFTVRGKP-TLEDLEQFSEKFYCSCYSTLSCKEKADV KDTDAVDV-CIADGVCIDAFLKPPMETEEPQIFYNASPSTLS (SEQ ID NO: 3306).

In any of the methods provided herein, the anti-hyaluronan agent can be an agent that degrades hyaluronan or can be an agent that inhibits the synthesis of hyaluronan. For example, the anti-hyaluronan agent can be a hyaluronan degrading enzyme. In another example, the anti-hyaluronan agent or is an agent that inhibits hyaluronan synthesis. For example, the anti-hyaluronan agent is an agent that inhibits hyaluronan synthesis such as a sense or antisense nucleic acid molecule against an HA synthase or is a small molecule drug. For example, an anti-hyaluronan agent is 4-methylumbelliferone (MU) or a derivative thereof, or leflunomide or a derivative thereof. Such derivatives include, for example, a derivative of 4-methylumbelliferone (MU) that is 6,7-dihydroxy-4-methyl coumarin or 5,7-dihydroxy-4-methyl coumarin.

In further examples of the methods provided herein, the hyaluronan degrading enzyme is a hyaluronidase. In some examples, the hyaluronan-degrading enzyme is a PH20 hyaluronidase or truncated form thereof to lacking a C-terminal glycosylphosphatidylinositol (GPI) attachment site or a portion of the GPI attachment site. In specific examples, the hyaluronidase is a PH20 selected from a human, monkey, bovine, ovine, rat, mouse or guinea pig PH20. For example, the hyaluronan-degrading enzyme is a human PH20 hyaluronidase that is neutral active and N-glycosylated and is selected from among (a) a hyaluronidase polypeptide that is a full-length PH20 or is a C-terminal truncated form of the PH20, wherein the truncated form includes at least amino acid residues 36-464 of SEQ ID NO: 139, such as 36-481, 36-482, 36-483, where the full-length PH20 has the sequence of amino acids set forth in SEQ ID NO: 139; or (b) a hyaluronidase polypeptide comprising a sequence of amino acids having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with the polypeptide or truncated form of sequence of amino acids set forth in SEQ ID NO: 139; or (c) a hyaluronidase polypeptide of (a) or (b) comprising amino acid substitutions, whereby the hyaluronidase polypeptide has a sequence of amino acids having at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity with the polypeptide set forth in SEQ ID NO: 139 or the with the corresponding truncated forms thereof. In exemplary examples, the hyaluronan-degrading enzyme is a PH20 that comprises a composition designated rHuPH20.

In other examples, the anti-hyaluronan agent is a hyaluronan degrading enzyme that is modified by conjugation to a polymer. The polymer can be a PEG and the anti-hyaluronan agent a PEGylated hyaluronan degrading enzyme. Hence, in some examples of the methods provided herein the hyaluronan-degrading enzyme is modified by conjugation to a polymer. For example, the hyaluronan-degrading enzyme is conjugated to a PEG, thus the hyaluronan degrading enzyme is PEGylated. In an exemplary example, the hyaluronan-degrading enzyme is a PEGylated PH20 enzyme (PEGPH20). In the methods provided herein, the corticosteroid can be a glucocorticoid that is selected from among cortisones, dexamethasones, hydrocortisones, methylprednisolones, prednisolones and prednisones.

Chondroitinases

Chondroitinases are enzymes found throughout the animal kingdom which degrade glycosaminoglycans, specifi-

cally chondroitins and chondroitin sulfates, through an endoglycosidase reaction. In some embodiments the chondroitinase is a mammalian chondroitinase. In some embodiments the chondroitinase is a recombinant human chondroitinase. In some embodiments the chondroitinase is HYAL4. Other exemplary chondroitinases include chondroitinase ABC (derived from *Proteus vulgaris*; Japanese Patent Application Laid-open No 6-153947, T. Yamagata et al. J. Biol. Chem., 243, 1523 (1968), S. Suzuki et al, J. Biol. Chem., 243, 1543 (1968)), chondroitinase AC (derived from *Flavobacterium heparinum*; T. Yamagata et al., J. Biol. Chem., 243, 1523 (1968)), chondroitinase AC II (derived from *Arthrobacter aurescens*; K. Hiyama, and S. Okada, J. Biol. Chem., 250, 1824 (1975), K. Hiyama and S. Okada, J. Biochem. (Tokyo), 80, 1201 (1976)), Hyaluronidase ACIII (derived from *Flavobacterium* sp. Hp102; Hirofumi Miyazono et al., Seikagaku, 61, 1023 (1989)), chondroitinase B (derived from *Flavobacterium heparinum*; Y. M. Michelacci and C. P. Dietrich, Biochem. Biophys. Res. Commun., 56, 973 (1974), Y. M. Michelacci and C. P. Dietrich, Biochem. J., 151, 121 (1975), Kenichi Maeyama et al, Seikagaku, 57, 1189 (1985)), chondroitinase C (derived from *Flavobacterium* sp. Hp102; Hirofumi Miyazono et al, Seikagaku, 61, 1023 (1939)), and the like.

Matrix Metalloproteinases

Matrix metalloproteases (MMPs) are zinc-dependent endopeptidases that are the major proteases involved in extracellular matrix (ECM) degradation. MMPs are capable of degrading a wide range of extracellular molecules and a number of bioactive molecules. Twenty-four MMP genes have been identified in humans, which can be organized into six groups based on domain organization and substrate preference: Collagenases (MMP-1, -8 and -13), Gelatinases (MMP-2 and MMP-9), Stromelysins (MMP-3, -10 and -11), Matrilysin (MMP-7 and MMP-26), Membrane-type (MT)-MMPs (MMP-14, -15, -16, -17, -24 and -25) and others (MMP-12, -19, -20, -21, -23, -27 and -28). In some embodiments, the stromal modifying moiety is a human recombinant MMP (e.g., MMP-1, -2, -3, -4, -5, -6, -7, -8, -9, 10, -11, -12, -13, -14, 15, -15, -17, -18, -19, 20, -21, -22, -23, or -24).

Collagenases

The three mammalian collagenases (MMP-1, -8, and -13) are the principal secreted endopeptidases capable of cleaving collagenous extracellular matrix. In addition to fibrillar collagens, collagenases can cleave several other matrix and non-matrix proteins including growth factors. Collagenases are synthesized as inactive pro-forms, and once activated, their activity is inhibited by specific tissue inhibitors of metalloproteinases, TIMPs, as well as by non-specific proteinase inhibitors (Ala-aho R et al. Biochimie. Collagenases in cancer. 2005 March-April; 87(3-4):273-86). In some embodiments, the stromal modifying moiety is a collagenase. In some embodiments, the collagenase is a human recombinant collagenase. In some embodiments, the collagenase is MMP-1. In some embodiments, the collagenase is MMP-8. In some embodiments, the collagenase is MMP-13.

Macrophage Metalloelastase

Macrophage metalloelastase (MME), also known as MMP-12, is a member of the stromelysin subgroup of MMPs and catalyzes the hydrolysis of soluble and insoluble elastin and a broad selection of matrix and nonmatrix substrates including type IV collagen, fibronectin, laminin, vitronectin, entactin, heparan, and chondroitin sulfates (Erja Kerkela et al. Journal of Investigative Dermatology (2000) 114, 1113-1119; doi:10.1046/j.1523-1747.2000.00993). In some embodiments, the stromal modifying moiety is a MME. In some embodiments, the MME is a human recombinant MME. In some embodiments, the MME is MMP-12.

Additional Stromal Modifying Moieties

In some embodiments, the stromal modifying moiety causes one or more of: decreases the level or production of a stromal or extracellular matrix (ECM) component; decreases tumor fibrosis; increases interstitial tumor transport; improves tumor perfusion; expands the tumor microvasculature; decreases interstitial fluid pressure (IFP) in a tumor; or decreases or enhances penetration or diffusion of an agent, e.g., a cancer therapeutic or a cellular therapy, into a tumor or tumor vasculature.

In some embodiments, the stromal or ECM component decreased is chosen from a glycosaminoglycan or an extracellular protein, or a combination thereof. In some embodiments, the glycosaminoglycan is chosen from hyaluronan (also known as hyaluronic acid or HA), chondroitin sulfate, chondroitin, dermatan sulfate, heparin, heparin sulfate, entactin, tenascin, aggrecan and keratin sulfate. In some embodiments, the extracellular protein is chosen from collagen, laminin, elastin, fibrinogen, fibronectin, or vitronectin. In some embodiments, the stromal modifying moiety includes an enzyme molecule that degrades a tumor stroma or extracellular matrix (ECM). In some embodiments, the enzyme molecule is chosen from a hyaluronidase molecule, a collagenase molecule, a chondroitinase molecule, a matrix metalloproteinase molecule (e.g., macrophage metalloelastase), or a variant (e.g., a fragment) of any of the aforesaid. The term "enzyme molecule" includes a full length, a fragment or a variant of the enzyme, e.g., an enzyme variant that retains at least one functional property of the naturally-occurring enzyme.

In some embodiments, the stromal modifying moiety decreases the level or production of hyaluronic acid. In other embodiments, the stromal modifying moiety comprises a hyaluronan degrading enzyme, an agent that inhibits hyaluronan synthesis, or an antibody molecule against hyaluronic acid.

In some embodiments, the hyaluronan degrading enzyme is a hyaluronidase molecule, e.g., a full length or a variant (e.g., fragment thereof) thereof. In some embodiments, the hyaluronan degrading enzyme is active in neutral or acidic pH, e.g., pH of about 4-5. In some embodiments, the hyaluronidase molecule is a mammalian hyaluronidase molecule, e.g., a recombinant human hyaluronidase molecule, e.g., a full length or a variant (e.g., fragment thereof, e.g., a truncated form) thereof. In some embodiments, the hyaluronidase molecule is chosen from HYAL1, HYAL2, or PH-20/SPAM1, or a variant thereof (e.g., a truncated form thereof). In some embodiments, the truncated form lacks a C-terminal glycosylphosphatidylinositol (GPI) attachment site or a portion of the GPI attachment site. In some embodiments, the hyaluronidase molecule is glycosylated, e.g., comprises at least one N-linked glycan.

In some embodiments, the hyaluronidase molecule comprises the amino acid sequence: LNFRAPPVIPNVPFL-WAWNAPSEFCLGKFDEPLDMSLFSFIGSPRI-NATGQGVTIFYVDRL GYYPYIDSITGVTVNGGIPQKIS-LQDHLDKAKKDITFYMPVDNLGMAVIDWEE-WRPTW ARNWKPKDVYKNRSIELVQQQNVQLSL-TEATEKAKQEFEKAGKDFLVETIKLGKLLRP NHLWGYYLFPDCYNHHYKKPGYNGSCFN-VEIKRNDDLSWLWNESTALYPSIYLNTQQS PVAAT-LYVRNRVREAIRVSKIPDAKSPLPVFAY-TRIVFTDQVLKFLSQDELVYTFGETVA LGASGIVIWGTLSIMRSMKSCLLLDNYMETILNPYI-

INVTLAAKMCSQVLCQEQGVCIRK
NWNSSDYLHLNPDNFAIQLEKGGKFTVRGKP-
TLEDLEQFSEKFYCSCYSTLSCKEKADV KDTDAVDV-
CIADGVCIDAFLKPPMETEEPQIFYNASPSTLS (SEQ ID NO:3311), or a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3311.

In some embodiments, the hyaluronidase molecule comprises:

(i) the amino acid sequence of 36-464 of SEQ ID NO: 3311;

(ii) the amino acid sequence of 36-481, 36-482, or 36-483 of PH20, wherein PH20 has the sequence of amino acids set forth in SEQ ID NO: 3311; or

(iii) an amino acid sequence having at least 95% to 100% sequence identity to the polypeptide or truncated form of sequence of amino acids set forth in SEQ ID NO: 3311; or

(iv) an amino acid sequence having 30, 20, 10, 5 or fewer amino acid substitutions to the amino acid sequence set forth in SEQ ID NO: 3311. In some embodiments, the hyaluronidase molecule comprises an amino acid sequence at least 95% (e.g., at least 95%, 96%, 97%, 98%, 99%, 100%) identical to the amino acid sequence of SEQ ID NO: 3311. In some embodiments, the hyaluronidase molecule is encoded by a nucleotide sequence at least 95% (e.g., at least 96%, 97%, 98%, 99%, 100%) identical to the nucleotide sequence of SEQ ID NO: 3311.

In some embodiments, the hyaluronidase molecule is PH20, e.g., rHuPH20. In some embodiments, the hyaluronidase molecule is HYAL1 and comprises the amino acid sequence: FRGPLLPNRPFTTVWNANTQWCLER-
HGVDVDVSVFDVVANPGQTFRGPDMTIFYSSQG
TYPYYTPTGEPVFGGLPQNASLIAHLARTFQDILAAI-
PAPDFSGLAVIDWEAWRPRWAFN
WDTKDIYRQRSRALVQAQHPDWPAPQVEAV-
AQDQFQGAARAWMAGTLQLGRALRPR
GLWGFYGFPDCYNYDFLSPNYTGQCPSGI-
RAQNDQLGWLWGQSRALYPSIYMPAVLEG
TGKSQMYVQHRVAEAFRVAVAAGDPNLPVLPYVQI-
FYDTTNHFLPLDELEHSLGESAA QGAAGVVLWVS-
WENTRTKESCQAIKEYMDTTLGP-
FILNVTSGALLCSQALCSGHGRCV
RRTSHPKALLLLNPASFSIQLTPGGGPLSLR-
GALSLEDQAQMAVEFKCRCYPGWQAPWC ERKSMW (SEQ ID NO: 3312), or a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3312.

In some embodiments, the hyaluronan degrading enzyme, e.g., the hyaluronidase molecule, further comprises a polymer, e.g., is conjugated to a polymer, e.g., PEG. In some embodiments, the hyaluronan-degrading enzyme is a PEGylated PH20 enzyme (PEGPH20). In some embodiments, the hyaluronan degrading enzyme, e.g., the hyaluronidase molecule, further comprises an immunoglobulin chain constant region (e.g., Fc region) chosen from, e.g., the heavy chain constant regions of IgG1, IgG2, IgG3, and IgG4, more particularly, the heavy chain constant region of human IgG1, IgG2, IgG3, or IgG4. In some embodiments, the immunoglobulin constant region (e.g., the Fc region) is linked, e.g., covalently linked to, the hyaluronan degrading enzyme, e.g., the hyaluronidase molecule. In some embodiments, the immunoglobulin chain constant region (e.g., Fc region) is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function. In some embodiments, the hyaluronan degrading enzyme, e.g., the hyaluronidase molecule forms a dimer.

In some embodiments, the stromal modifying moiety comprises an inhibitor of the synthesis of hyaluronan, e.g., an HA synthase. In some embodiments, the inhibitor comprises a sense or an antisense nucleic acid molecule against an HA synthase or is a small molecule drug. In some embodiments, the inhibitor is 4-methylumbelliferone (MU) or a derivative thereof (e.g., 6,7-dihydroxy-4-methyl coumarin or 5,7-dihydroxy-4-methyl coumarin), or leflunomide or a derivative thereof.

In some embodiments, the stromal modifying moiety comprises antibody molecule against hyaluronic acid.

In some embodiments, the stromal modifying moiety comprises a collagenase molecule, e.g., a mammalian collagenase molecule, or a variant (e.g., fragment) thereof. In some embodiments, the collagenase molecule is collagenase molecule IV, e.g., comprising the amino acid sequence of:
YNFFPRKPKWDKNQITYRIIGYTPDLDPETVDDA-
FARAFQVWSDVTPLRFSRIHDGEADI MINFGR-
WEHGDGYPFDGKDGLLAHAFAPGTGVGGDSHFDD-
DELWTLGEGQVVRVKY
GNADGEYCKFPFLFNGKEYNSCTDTGRSDGFLWC-
STTYNFEKDGKYGFCPHEALFTMG GNAEGQPCKFP-
FRFQGTSYDSCTTEGRTDGYRWCGTTEDY-
DRDKKYGFCPETAMSTVG
GNSEGAPCVFPFTFLGNKYESCTSAGRSDGKMW-
CATTANYDDDRKWGFCPDQGYSLF LVAA-
HEFGHAMGLEHSQDPGALMAPIYTYTKNFRLSQD-
DIKGIQELYGASPDIDLGTGP
TPTLGPVTPEICKQDIVFDGIAQIRGE-
IFFFKDRFIWRTVTPRDKPMGPLLVATFWPELPEK
IDAVYEAPQEEKAVFFAGNEYWIYSASTLER-
GYPKPLTSLGLPPDVQRVDAAFNWSKNK KTYIF-
AGDKFWRYNEVKKKMDPGFPKLIADAWNAIPDNL-
DAVVDLQGGGHSYFFKGA
YYLKLENQSLKSVKFGSIKSDWLGC (SEQ ID NO: 3313), or a fragment thereof, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) to the amino acid sequence of SEQ ID NO: 3313.

Linkers

The multispecific or multifunctional molecule disclosed herein can further include a linker, e.g., a linker between one or more of: the antigen binding domain and the cytokine molecule, the antigen binding domain and the immune cell engager, the antigen binding domain and the stromal modifying moiety, the cytokine molecule and the immune cell engager, the cytokine molecule and the stromal modifying moiety, the immune cell engager and the stromal modifying moiety, the antigen binding domain and the immunoglobulin chain constant region, the cytokine molecule and the immunoglobulin chain constant region, the immune cell engager and the immunoglobulin chain constant region, or the stromal modifying moiety and the immunoglobulin chain constant region. In embodiments, the linker is chosen from: a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, or a non-helical linker, or a combination thereof.

In one embodiment, the multispecific molecule can include one, two, three or four linkers, e.g., a peptide linker. In one embodiment, the peptide linker includes Gly and Ser. In some embodiments, the peptide linker is selected from GGGGS (SEQ ID NO: 3307); GGGGSGGGGS (SEQ ID NO: 3308); GGGGSGGGGSGGGGS (SEQ ID NO: 3309); and DVPSGPGGGGGSGGGGS (SEQ ID NO: 3310). In some embodiments, the peptide linker is a A(EAAAK)nA (SEQ ID NO: 3437) family of linkers (e.g., as described in Protein Eng. (2001) 14 (8): 529-532). These are stiff helical linkers with n ranging from 2-5. In some embodiments, the peptide linker is selected from AEAAAKEAAAKAAA (SEQ ID NO: 3314); AEAAAKEAAAKEAAAKAAA (SEQ ID NO: 3315); AEAAAKEAAAKEAAAKEAAAKAAA (SEQ ID NO: 3316); and AEAAAKEAAAKEAAAKEAAAKEAAAKAAA (SEQ ID NO: 3317).

Nucleic Acids

Nucleic acids encoding the aforementioned antibody molecules, e.g., anti-TCRβV antibody molecules, multispecific or multifunctional molecules are also disclosed.

In certain embodiments, the invention features nucleic acids comprising nucleotide sequences that encode heavy and light chain variable regions and CDRs or hypervariable loops of the antibody molecules, as described herein. For example, the invention features a first and second nucleic acid encoding heavy and light chain variable regions, respectively, of an antibody molecule chosen from one or more of the antibody molecules disclosed herein. The nucleic acid can comprise a nucleotide sequence as set forth in the tables herein, or a sequence substantially identical thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, or which differs by no more than 3, 6, 15, 30, or 45 nucleotides from the sequences shown in the tables herein.

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a heavy chain variable region having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, e.g., conserved substitutions). In other embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a light chain variable region having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, e.g., conserved substitutions). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs or hypervariable loops from heavy and light chain variable regions having an amino acid sequence as set forth in the tables herein, or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or having one or more substitutions, e.g., conserved substitutions).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a heavy chain variable region having the nucleotide sequence as set forth in the tables herein, a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, or three CDRs or hypervariable loops from a light chain variable region having the nucleotide sequence as set forth in the tables herein, or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein). In yet another embodiment, the nucleic acid can comprise a nucleotide sequence encoding at least one, two, three, four, five, or six CDRs or hypervariable loops from heavy and light chain variable regions having the nucleotide sequence as set forth in the tables herein, or a sequence substantially homologous thereto (e.g., a sequence at least about 85%, 90%, 95%, 99% or more identical thereto, and/or capable of hybridizing under the stringency conditions described herein).

In certain embodiments, the nucleic acid can comprise a nucleotide sequence encoding a cytokine molecule, an immune cell engager, or a stromal modifying moiety disclosed herein.

In another aspect, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell, as described in more detail hereinbelow.

Vectors

Further provided herein are vectors comprising the nucleotide sequences encoding antibody molecules, e.g., anti-TCRβV antibody molecules, or a multispecific or multifunctional molecule described herein. In one embodiment, the vectors comprise nucleic acid sequences encoding antibody molecules, e.g., anti-TCRβV antibody molecules, or multispecific or multifunctional molecule described herein. In one embodiment, the vectors comprise the nucleotide sequences described herein. The vectors include, but are not limited to, a virus, plasmid, cosmid, lambda phage or a yeast artificial chromosome (YAC).

Numerous vector systems can be employed. For example, one class of vectors utilizes DNA elements which are derived from animal viruses such as, for example, bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (Rous Sarcoma Virus, MMTV or MOMLV) or SV40 virus. Another class of vectors utilizes RNA elements derived from RNA viruses such as Semliki Forest virus, Eastern Equine Encephalitis virus and Flaviviruses.

Additionally, cells which have stably integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow for the selection of transfected host cells. The marker may provide, for example, prototropy to an auxotrophic host, biocide resistance (e.g., antibiotics), or resistance to heavy metals such as copper, or the like. The selectable marker gene can be either directly linked to the DNA sequences to be expressed, or introduced into the same cell by cotransformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcriptional promoters, enhancers, and termination signals.

Once the expression vector or DNA sequence containing the constructs has been prepared for expression, the expression vectors may be transfected or introduced into an appropriate host cell. Various techniques may be employed to achieve this, such as, for example, protoplast fusion, calcium phosphate precipitation, electroporation, retroviral transduction, viral transfection, gene gun, lipid based trans-

fection or other conventional techniques. In the case of protoplast fusion, the cells are grown in media and screened for the appropriate activity.

Methods and conditions for culturing the resulting transfected cells and for recovering the antibody molecule produced are known to those skilled in the art, and may be varied or optimized depending upon the specific expression vector and mammalian host cell employed, based upon the present description.

Cells

In another aspect, the application features host cells and vectors containing the nucleic acids described herein. The nucleic acids may be present in a single vector or separate vectors present in the same host cell or separate host cell. The host cell can be a eukaryotic cell, e.g., a mammalian cell, an insect cell, a yeast cell, or a prokaryotic cell, e.g., *E. coli*. For example, the mammalian cell can be a cultured cell or a cell line. Exemplary mammalian cells include lymphocytic cell lines (e.g., NSO), Chinese hamster ovary cells (CHO), COS cells, oocyte cells, and cells from a transgenic animal, e.g., mammary epithelial cell.

The invention also provides host cells comprising a nucleic acid encoding an antibody molecule as described herein.

In one embodiment, the host cells are genetically engineered to comprise nucleic acids encoding the antibody molecule.

In one embodiment, the host cells are genetically engineered by using an expression cassette. The phrase "expression cassette," refers to nucleotide sequences, which are capable of affecting expression of a gene in hosts compatible with such sequences. Such cassettes may include a promoter, an open reading frame with or without introns, and a termination signal. Additional factors necessary or helpful in effecting expression may also be used, such as, for example, an inducible promoter.

The invention also provides host cells comprising the vectors described herein.

The cell can be, but is not limited to, a eukaryotic cell, a bacterial cell, an insect cell, or a human cell. Suitable eukaryotic cells include, but are not limited to, Vero cells, HeLa cells, COS cells, CHO cells, HEK293 cells, BHK cells and MDCKII cells. Suitable insect cells include, but are not limited to, Sf9 cells.

Method of Expanding Cells with Anti-TCRVB Antibodies

Any of the compositions and methods described herein can be used to expand an immune cell population. An immune cell provided herein includes an immune cell derived from a hematopoietic stem cell or an immune cell derived from a non-hematopoietic stem cell, e.g., by differentiation or de-differentiation.

An immune cell includes a hematopoietic stem cell, progeny thereof and/or cells that have differentiated from said HSC, e.g., lymphoid cells or myeloid cells. An immune cell can be an adaptive immune cell or an innate immune cell. Examples of immune cells include T cells, B cells, Natural Killer cells, Natural Killer T cells, neutrophils, dendritic cells, monocytes, macrophages, and granulocytes.

In some embodiments of any of the methods of compositions disclosed herein, an immune cell is a T cell. In some embodiments, a T cell includes a CD4+ T cell, a CD8+ T cell, a TCR alpha-beta T cell, a TCR gamma-delta T cell. In some embodiments, a T cell comprises a memory T cell (e.g., a central memory T cell, or an effector memory T cell (e.g., a TEMRA) or an effector T cell. In some embodiments, a T cell comprises a tumor infiltrating lymphocyte (TIL).

In some embodiments of any of the methods of compositions disclosed herein, an immune cell is an NK cell.

In some embodiments of any of the methods of compositions disclosed herein, an immune cell is a TIL. TILs are immune cells (e.g., T cells, B cells or NK cells) that can be found in a tumor or around a tumor (e.g., in the stroma or tumor microenvironment of a tumor), e.g., a solid tumor, e.g., as described herein. TILs can be obtained from a sample from a subject having cancer, e.g., a biopsy or a surgical sample. In some embodiments, TILs can be expanded using a method disclosed herein. In some embodiments, a population of expanded TILs, e.g., expanded using a method disclosed herein, can be administered to a subject to treat a disease, e.g., a cancer.

In certain aspects of the present disclosure, immune cells, e.g., T cells (e.g., TILs), can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled artisan, such as Ficoll™ separation. In one aspect, cells from the circulating blood of an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and platelets. In one aspect, the cells collected by apheresis may be washed to remove the plasma fraction and, optionally, to place the cells in an appropriate buffer or media for subsequent processing steps. In one embodiment, the cells are washed with phosphate buffered saline (PBS). In an alternative embodiment, the wash solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. The methods described herein can include more than one selection step, e.g., more than one depletion step.

In one embodiment, the methods of the application can utilize culture media conditions comprising DMEM, DMEM F12, RPMI 1640, and/or AIM V media. The media can be supplemented with glutamine, HEPES buffer (e.g., 10 mM), serum (e.g., heat-inactivated serum, e.g., 10%), and/or beta mercaptoethanol (e.g., 55 uM). IN some embodiments, the culture conditions disclosed herein comprise one or more supplements, cytokines, growth factors, or hormones. In some embodiments, the culture condition comprises one or more of IL-2, IL-15, or IL-7, or a combination thereof.

Immune effector cells such as T cells may be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; or 6,905,680. Generally, a population of immune cells, may be expanded by contact with an agent that stimulates a CD3/TCR complex associated signal and a ligand that stimulates a costimulatory molecule on the surface of the T cells; and/or by contact with a cytokine, e.g., IL-2, IL-15 or IL-7. T cell expansion protocols can also include stimulation, such as by contact with an anti-CD3 antibody, or antigen-binding fragment thereof, or an anti-CD2 antibody immobilized on a surface, or by contact with a protein kinase C activator (e.g., bryostatin) in conjunction with a calcium ionophore. For example, a population of T cells can be contacted with an anti-CD3 antibody and an anti-CD28 antibody, under conditions appropriate for stimulating proliferation of the T cells. To stimulate proliferation of either CD4+ T cells or CD8+ T cells, an anti-CD3 antibody and an anti-CD28 antibody can be used. Examples of an anti-CD28 antibody include 9.3, B-T3, XR-CD28 (Diaclone, Besancon, France) can be used as can other methods commonly known in the art (Berg et al., Transplant Proc. 30(8):3975-3977, 1998; Haanen et al., J. Exp. Med. 190(9):13191328, 1999; Garland et al., J. Immunol Meth. 227(1-2):53-63, 1999).

A TIL population can also be expanded by methods known in the art. For example, a population of TILs can be expanded as described in Hall et al., *Journal for Immuno-Therapy of Cancer* (2016) 4:61, the entire contents of which are hereby incorporated by reference. Briefly, TILs can be isolated from a sample by mechanical and/or physical digestion. The resultant TIL population can be stimulated with an anti-CD3 antibody in the presence of non-dividing feeder cells. In some embodiments, the TIL population can be cultured, e.g., expanded, in the presence of IL-2, e.g., human IL-2. In some embodiments, the TIL cells can be cultured, e.g., expanded fora period of at least 1-21 days, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or 21 days.

As disclosed herein, in some embodiments, an immune cell population (e.g., a T cell (e.g., a T_{EMRA} cell or a TIL population) can be expanded by contacting the immune cell population with an anti-TCRVB antibody, e.g., as described herein.

In some embodiments, the expansion occurs in vivo, e.g., in a subject. In some embodiments, a subject is administered an anti-TCRβV antibody molecule disclosed herein resulting in expansion of immune cells in vivo.

In some embodiments, the expansion occurs ex vivo, e.g., in vitro. In some embodiments, cells from a subject, e.g., T cells, e.g., TIL cells, are expanded in vitro with an anti-TCRβV antibody molecule disclosed herein. In some embodiments, the expanded TILs are administered to the subject to treat a disease or a symptom of a disease.

In some embodiments, a method of expansion disclosed herein results in an expansion of at least 1.1-10 fold, 10-20 fold, or 20-50 fold expansion. In some embodiments, the expansion is at least 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45 or 50 fold expansion.

In some embodiments, a method of expansion disclosed herein comprises culturing, e.g., expanding, the cells for at least about 4 hours, 6 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 22 hours. In some embodiments, a method of expansion disclosed herein comprises culturing, e.g., expanding, the cells for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 1,6 17, 18, 19, 20 or 21 days. In some embodiments, a method of expansion disclosed herein comprises culturing, e.g., expanding, the cells for at least about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks or 8 weeks.

In some embodiments, a method of expansion disclosed herein is performed on immune cells obtained from a healthy subject.

In some embodiments, a method of expansion disclosed herein is performed on immune cells (e.g., TILs) obtained from a subject having a disease, e.g., a cancer, e.g., a solid tumor as disclosed herein.

In some embodiments, a method of expansion disclosed herein further comprises contacting the population of cells with an agent, that promotes, e.g., increases, immune cell expansion. In some embodiments, the agent comprises an immune checkpoint inhibitor, e.g., a PD-1 inhibitor, a LAG-3 inhibitor, a CTLA4 inhibitor, or a TIM-3 inhibitor. In some embodiments, the agent comprises a 4-1BB agonist, e.g., an anti-4-1BB antibody.

Without wishing to be bound by theory, it is believed that an anti-TCRβV antibody molecule disclosed herein can expand, e.g., selectively or preferentially expand, T cells expressing a T cell receptor (TCR) comprising a TCR alpha and/or TCR beta molecule, e.g., TCR alpha-beta T cells (αβ T cells). In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not expand, or induce proliferation of T cells expressing a TCR comprising a TCR gamma and/or TCR delta molecule, e.g., TCR gamma-delta T cells (γδ T cells). In some embodiments, an anti-TCRβV antibody molecule disclosed herein, selectively or preferentially expands αβ T cells over γδ T cells.

Without wishing to be bound by theory, it is believed that, in some embodiments, γδ T cells are associated with cytokine release syndrome (CRS) and/or neurotoxicity (NT). In some embodiments, an anti-TCRβV antibody molecule disclosed herein results in selective expansion of non-γδ T cells, e.g., expansion of αβ T cells, thus reducing CRS and/or NT.

In some embodiments, any of the compositions or methods disclosed herein result in an immune cell population having a reduction of, e.g., depletion of, γδ T cells. In some embodiments, the immune cell population is contacted with an agent that reduces, e.g., inhibits or depletes, γδ T cells, e.g., an anti-IL-17 antibody or an agent that binds to a TCR gamma and/or TCR delta molecule.

Uses and Combination Therapies

Methods described herein include treating a cancer in a subject by using an anti-TCRβV antibody molecule, a multispecific or multifunctional molecule described herein, e.g., using a pharmaceutical composition described herein. Also provided are methods for reducing or ameliorating a symptom of a cancer in a subject, as well as methods for inhibiting the growth of a cancer and/or killing one or more cancer cells. In embodiments, the methods described herein decrease the size of a tumor and/or decrease the number of cancer cells in a subject administered with a described herein or a pharmaceutical composition described herein.

In embodiments, the cancer is a hematological cancer. In embodiments, the hematological cancer is a leukemia or a lymphoma. As used herein, a "hematologic cancer" refers to a tumor of the hematopoietic or lymphoid tissues, e.g., a tumor that affects blood, bone marrow, or lymph nodes. Exemplary hematologic malignancies include, but are not limited to, leukemia (e.g., acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), hairy cell leukemia, acute monocytic leukemia (AMoL), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), or large granular lymphocytic leukemia), lymphoma (e.g., AIDS-related lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma (e.g., classical Hodgkin lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma), mycosis fungoides, non-Hodgkin lymphoma (e.g., B-cell non-Hodgkin lymphoma (e.g., Burkitt lymphoma, small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, or mantle cell lymphoma) or T-cell non-Hodgkin lymphoma (mycosis fungoides, anaplastic large cell lymphoma, or precursor T-lymphoblastic lymphoma)), primary central nervous system lymphoma, Sezary syndrome, Waldenstrom macroglobulinemia), chronic myeloproliferative neoplasm, Langerhans cell histiocytosis, multiple myeloma/plasma cell neoplasm, myelodysplastic syndrome, or myelodysplastic/myeloproliferative neoplasm.

In embodiments, the cancer is a myeloproliferative neoplasm, e.g., primary or idiopathic myelofibrosis (MF), essential thrombocytosis (ET), polycythemia vera (PV), or chronic myelogenous leukemia (CIVIL). In embodiments, the cancer is myelofibrosis. In embodiments, the subject has myelofibrosis. In embodiments, the subject has a calreticulin mutation, e.g., a calreticulin mutation disclosed herein. In

embodiments, the subject does not have the JAK2-V617F mutation. In embodiments, the subject has the JAK2-V617F mutation. In embodiments, the subject has a MPL mutation. In embodiments, the subject does not have a MPL mutation.

In embodiments, the cancer is a solid cancer. Exemplary solid cancers include, but are not limited to, ovarian cancer, rectal cancer, stomach cancer, testicular cancer, cancer of the anal region, uterine cancer, colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, Kaposi's sarcoma, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, brain stem glioma, pituitary adenoma, epidermoid cancer, carcinoma of the cervix squamous cell cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the vagina, sarcoma of soft tissue, cancer of the urethra, carcinoma of the vulva, cancer of the penis, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, spinal axis tumor, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, metastatic lesions of said cancers, or combinations thereof.

In embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecules (or pharmaceutical composition) are administered in a manner appropriate to the disease to be treated or prevented. The quantity and frequency of administration will be determined by such factors as the condition of the patient, and the type and severity of the patient's disease. Appropriate dosages may be determined by clinical trials. For example, when "an effective amount" or "a therapeutic amount" is indicated, the precise amount of the pharmaceutical composition (or multispecific or multifunctional molecules) to be administered can be determined by a physician with consideration of individual differences in tumor size, extent of infection or metastasis, age, weight, and condition of the subject. In embodiments, the pharmaceutical composition described herein can be administered at a dosage of 10^4 to 10^9 cells/kg body weight, e.g., 10^5 to 10^6 cells/kg body weight, including all integer values within those ranges. In embodiments, the pharmaceutical composition described herein can be administered multiple times at these dosages. In embodiments, the pharmaceutical composition described herein can be administered using infusion techniques described in immunotherapy (see, e.g., Rosenberg et al., New Eng. J. of Med. 319:1676, 1988).

In embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecules or pharmaceutical composition is administered to the subject parentally. In embodiments, the cells are administered to the subject intravenously, subcutaneously, intratumorally, intranodally, intramuscularly, intradermally, or intraperitoneally. In embodiments, the cells are administered, e.g., injected, directly into a tumor or lymph node. In embodiments, the cells are administered as an infusion (e.g., as described in Rosenberg et al., New Eng. J. of Med. 319:1676, 1988) or an intravenous push. In embodiments, the cells are administered as an injectable depot formulation.

In embodiments, the subject is a mammal. In embodiments, the subject is a human, monkey, pig, dog, cat, cow, sheep, goat, rabbit, rat, or mouse. In embodiments, the subject is a human. In embodiments, the subject is a pediatric subject, e.g., less than 18 years of age, e.g., less than 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less years of age. In embodiments, the subject is an adult, e.g., at least 18 years of age, e.g., at least 19, 20, 21, 22, 23, 24, 25, 25-30, 30-35, 35-40, 40-50, 50-60, 60-70, 70-80, or 80-90 years of age.

Methods of Cancer Treatment

Methods described herein include treating a cancer in a subject by using an anti-TCRβV antibody molecule, e.g., using a pharmaceutical composition described herein. Also provided are methods for reducing or ameliorating a symptom of a cancer in a subject, as well as methods for inhibiting the growth of a cancer and/or killing one or more cancer cells. In embodiments, the methods described herein decrease the size of a tumor and/or decrease the number of cancer cells in a subject administered with a described herein or a pharmaceutical composition described herein.

Disclosed herein are methods of treating a subject having a cancer comprising acquiring a status of one or more TCRBV molecules in a subject. In some embodiments, a higher, e.g., increased, level or activity of one or more TCRβV molecules in a subject, e.g., in a sample from a subject, is indicative of a bias, e.g., a preferential expansion, e.g., clonal expansion, of T cells expressing said one or more TCRβV molecules in the subject.

Without wishing to be bound by theory, it is believed that a biased T cell population, e.g., a T cell population expressing a TCRβV molecule, is antigen-specific for a disease antigen, e.g., a cancer antigen (Wang C Y, et al., *Int J Oncol.* (2016) 48(6):2247-56). In some embodiments, the cancer antigen comprises a cancer associated antigen or a neoantigen. In some embodiments, a subject having a cancer, e.g., as disclosed herein, has a higher, e.g., increased, level or activity of one or more TCRβV molecules associated with the cancer. In some embodiments, the TCRβV molecule is associated with, e.g., recognizes, a cancer antigen, e.g., a cancer associated antigen or a neoantigen.

Accordingly, disclosed herein are methods of expanding an immune effector cell population obtained from a subject, comprising acquiring a status of one or more TCRβV molecules in a sample from the subject, comprising contacting said immune effector cell population with an anti-TCRβV antibody molecule disclosed herein, e.g., an anti-TCRβV antibody molecule that binds to the same TCRβV molecule that is higher, e.g., increased in the immune effector cell population in the sample from the subject. In some embodiments, contacting the population of immune effector cells (e.g., comprising T cells that express one or more TCRβV molecules) with an anti-TCRβV molecule results in expansion of the population of immune effector cells expressing one or more TCRβV molecules. In some embodiments, the expanded population, or a portion thereof, is administered to the subject (e.g., same subject from whom the immune effector cell population was obtained), to treat the cancer. In some embodiments, the expanded population, or a portion thereof, is administered to a different subject (e.g., not the same subject from whom the immune effector cell population was obtained), to treat the cancer.

Also disclosed herein, are methods of treating a subject having a cancer, comprising: acquiring a status of one or more TCRβV molecules in a sample from the subject, and determining whether the one or more TCRβV molecules is higher, e.g., increased, in a sample from the subject compared to a reference value, wherein responsive to said determination, administering to the subject an effective amount of an anti-TCRβV antibody molecule, e.g., an agonistic anti-TCRβV antibody molecule, e.g., as described herein.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has B-CLL. In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01; (ii) TCRβV5 subfamily comprising TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01; (iii) TCRβV3 subfamily comprising TCRβV3-1*01; (iv) TCRβV2 subfamily comprising TCRβV2*01; or (v) TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV6 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV6 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV5 subfamily comprising TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV5 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV5 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV3 subfamily comprising TCRβV3-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV3 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV3 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV2 subfamily comprising TCRβV2*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV2 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV2 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRBV molecule as described herein) that binds to one or more members of the TCRβV19 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV19 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has melanoma. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising the TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV6 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV6 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has DLBCL. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV13 subfamily comprising TCRβV13*01; (ii) TCRβV3 subfamily comprising TCRβV3-1*01; or (iii) TCRβV23 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV13 subfamily comprising TCRβV13*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV13 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV13 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV3 subfamily comprising TCRβV3-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV3 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV3 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV23 subfamily. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV23 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV23 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has CRC. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02; (ii) TCRβV12 subfamily comprising TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01; (iii) TCRβV16 subfamily comprising TCRβV16*01; or (iv) TCRβV21 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV19 subfamily. In some embodiments, administration

of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV19 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV12 subfamily comprising TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV12 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV12 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV16 subfamily comprising TCRβV16*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV16 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV16 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV21 subfamily. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV21 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV21 subfamily.

In some embodiments, acquiring a value for the status, e.g., presence, level and/or activity, of one or more TCRβV molecules comprises acquiring a measure of the T cell receptor (TCR) repertoire of a sample. In some embodiments, the value comprises a measure of the clonotype of a population of T cells in the sample.

In some embodiments, a value for the status of one or more TCRβV molecules is obtained, e.g., measured, using an assay described in Wang C Y, et al., Int J Oncol. (2016) 48(6):2247-56, the entire contents of which are hereby incorporated by reference.

In some embodiments, a value for the status of one or more TCRβV molecules is obtained, e.g., measured, using flow cytometry.

Combination Therapies

The anti-TCRβV antibody molecule, multispecific or multifunctional molecules disclosed herein can be used in combination with a second therapeutic agent or procedure.

In embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule and the second therapeutic agent or procedure are administered/performed after a subject has been diagnosed with a cancer, e.g., before the cancer has been eliminated from the subject. In embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule and the second therapeutic agent or procedure are administered/performed simultaneously or concurrently. For example, the delivery of one treatment is still occurring when the delivery of the second commences, e.g., there is an overlap in administration of the treatments. In other embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule and the second therapeutic agent or procedure are administered/performed sequentially. For example, the delivery of one treatment ceases before the delivery of the other treatment begins.

In embodiments, combination therapy can lead to more effective treatment than monotherapy with either agent alone. In embodiments, the combination of the first and second treatment is more effective (e.g., leads to a greater reduction in symptoms and/or cancer cells) than the first or second treatment alone. In embodiments, the combination therapy permits use of a lower dose of the first or the second treatment compared to the dose of the first or second treatment normally required to achieve similar effects when administered as a monotherapy. In embodiments, the combination therapy has a partially additive effect, wholly additive effect, or greater than additive effect.

In one embodiment, the anti-TCRBV antibody, multispecific or multifunctional molecule is administered in combination with a therapy, e.g., a cancer therapy (e.g., one or more of anti-cancer agents, immunotherapy, photodynamic therapy (PDT), surgery and/or radiation). The terms "chemotherapeutic," "chemotherapeutic agent," and "anti-cancer agent" are used interchangeably herein. The administration of the multispecific or multifunctional molecule and the therapy, e.g., the cancer therapy, can be sequential (with or without overlap) or simultaneous. Administration of the anti-TCRBV antibody, multispecific or multifunctional molecule can be continuous or intermittent during the course of therapy (e.g., cancer therapy). Certain therapies described herein can be used to treat cancers and non-cancerous diseases. For example, PDT efficacy can be enhanced in cancerous and non-cancerous conditions (e.g., tuberculosis) using the methods and compositions described herein (reviewed in, e.g., Agostinis, P. et al. (2011) *CA Cancer J. Clin.* 61:250-281).

Anti-Cancer Therapies

In other embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in combination with a low or small molecular weight chemotherapeutic agent. Exemplary low or small molecular weight chemotherapeutic agents include, but not limited to, 13-cis-retinoic acid (isotretinoin, ACCUTANE®), 2-CdA (2-chlorodeoxyadenosine, cladribine, LEUSTATIN™), 5-azacitidine (azacitidine, VIDAZA®), 5-fluorouracil (5-FU, fluorouracil, ADRUCIL®), 6-mercaptopurine (6-MP, mercaptopurine, PURINETHOL®), 6-TG (6-thioguanine, thioguanine, THIOGUANINE TABLOID®), abraxane (paclitaxel protein-bound), actinomycin-D (dactinomycin, COSMEGEN®), alitretinoin (PANRETIN®), all-trans-retinoic acid (ATRA, tretinoin, VESANOID®), altretamine (hexamethylmelamine, HMM, HEXALEN®), amethopterin (methotrexate, methotrexate sodium, MTX, TREXALL™, RHEUMATREX®), amifostine (ETHYOL®), arabinosylcytosine (Ara-C, cytarabine, CYTOSAR-U®), arsenic trioxide (TRISENOX®), asparaginase (Erwinia L-asparaginase, L-asparaginase, ELSPAR®, KIDROLASE®), BCNU (carmustine, BiCNU®), bendamustine (TREANDA®), bexarotene (TARGRETIN®), bleomycin (BLENOXANE®), busulfan (BUSULFEX®, MYLERAN®), calcium leucovorin (Citrovorum Factor, folinic acid, leucovorin), camptothecin-11 (CPT-11, irinotecan, CAMPTOSAR®), capecitabine (XELODA®), carboplatin (PARAPLATIN®), carmustine wafer (prolifeprospan 20 with carmustine implant, GLIADEL® wafer), CCI-779 (temsirolimus, TORISEL®), CCNU (lomustine, CeeNU), CDDP (cisplatin, PLATINOL®, PLATINOL-AQ®), chlorambucil (leukeran), cyclophosphamide (CYTOXAN®, NEOSAR®), dacarbazine (DIC, DTIC, imidazole carboxamide, DTIC-DOME®), daunomycin (daunorubicin, daunorubicin hydrochloride, rubidomycin hydrochloride, CERUBIDINE®), decitabine (DACOGEN®), dexrazoxane (ZINECARD®), DHAD (mitoxantrone, NOVANTRONE®), docetaxel (TAXOTERE®), doxorubicin (ADRIAMYCIN®,

RUBEX®), epirubicin (ELLENCE™), estramustine (EMCYT®), etoposide (VP-16, etoposide phosphate, TOPOSAR®, VEPESID®, ETOPOPHOS®), floxuridine (FUDR®), fludarabine (FLUDARA®), fluorouracil (cream) (CARAC™, EFUDEX®, FLUOROPLEX®), gemcitabine (GEMZAR®), hydroxyurea (HYDREA®, DROXIA™, MYLOCEL™), idarubicin (IDAMYCIN®), ifosfamide (IFEX®), ixabepilone (IXEMPRA™), LCR (leurocristine, vincristine, VCR, ONCOVIN®, VINCASAR PFS®), L-PAM (L-sarcolysin, melphalan, phenylalanine mustard, ALKERAN®), mechlorethamine (mechlorethamine hydrochloride, mustine, nitrogen mustard, MUSTARGEN®), mesna (MESNEX™), mitomycin (mitomycin-C, MTC, MUTAMYCIN®), nelarabine (ARRANON®), oxaliplatin (ELOXATIN™), paclitaxel (TAXOL®, ONXAL™), pegaspargase (PEG-L-asparaginase, ONCOSPAR®), PEMETREXED (ALIMTA®), pentostatin (NIPENT®), procarbazine (MATULANE®), streptozocin (ZANOSAR®), temozolomide (TEMODAR®), teniposide (VM-26, VUMON®), TESPA (thiophosphoamide, thiotepa, TSPA, THIOPLEX®), topotecan (HYCAMTIN®), vinblastine (vinblastine sulfate, vincaleukoblastine, VLB, ALKABAN-AQ®, VELBAN®), vinorelbine (vinorelbine tartrate, NAVELBINE®), and vorinostat (ZOLINZA®).

In another embodiment, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in conjunction with a biologic. Biologics useful in the treatment of cancers are known in the art and a binding molecule of the invention may be administered, for example, in conjunction with such known biologics. For example, the FDA has approved the following biologics for the treatment of breast cancer: HERCEPTIN® (trastuzumab, Genentech Inc., South San Francisco, Calif.; a humanized monoclonal antibody that has anti-tumor activity in HER2-positive breast cancer); FASLODEX® (fulvestrant, AstraZeneca Pharmaceuticals, LP, Wilmington, Del.; an estrogen-receptor antagonist used to treat breast cancer); ARIMIDEX® (anastrozole, AstraZeneca Pharmaceuticals, LP; a nonsteroidal aromatase inhibitor which blocks aromatase, an enzyme needed to make estrogen); Aromasin® (exemestane, Pfizer Inc., New York, N.Y.; an irreversible, steroidal aromatase inactivator used in the treatment of breast cancer); FEMARA® (letrozole, Novartis Pharmaceuticals, East Hanover, N.J.; a nonsteroidal aromatase inhibitor approved by the FDA to treat breast cancer); and NOLVADEX® (tamoxifen, AstraZeneca Pharmaceuticals, LP; a nonsteroidal antiestrogen approved by the FDA to treat breast cancer). Other biologics with which the binding molecules of the invention may be combined include: AVASTIN® (bevacizumab, Genentech Inc.; the first FDA-approved therapy designed to inhibit angiogenesis); and ZEVALIN® (ibritumomab tiuxetan, Biogen Idec, Cambridge, Mass.; a radiolabeled monoclonal antibody currently approved for the treatment of B-cell lymphomas).

In addition, the FDA has approved the following biologics for the treatment of colorectal cancer: AVASTIN®; ERBITUX® (cetuximab, ImClone Systems Inc., New York, N.Y., and Bristol-Myers Squibb, New York, N.Y.; is a monoclonal antibody directed against the epidermal growth factor receptor (EGFR)); GLEEVEC® (imatinib mesylate; a protein kinase inhibitor); and ERGAMISOL® (levamisole hydrochloride, Janssen Pharmaceutica Products, LP, Titusville, N.J.; an immunomodulator approved by the FDA in 1990 as an adjuvant treatment in combination with 5-fluorouracil after surgical resection in patients with Dukes' Stage C colon cancer).

For the treatment of lung cancer, exemplary biologics include TARCEVA® (erlotinib HCL, OSI Pharmaceuticals Inc., Melville, N.Y.; a small molecule designed to target the human epidermal growth factor receptor 1 (HER1) pathway).

For the treatment of multiple myeloma, exemplary biologics include VELCADE® Velcade (bortezomib, Millennium Pharmaceuticals, Cambridge Mass.; a proteasome inhibitor). Additional biologics include THALIDOMID® (thalidomide, Clegene Corporation, Warren, N.J.; an immunomodulatory agent and appears to have multiple actions, including the ability to inhibit the growth and survival of myeloma cells and anti-angiogenesis).

Additional exemplary cancer therapeutic antibodies include, but are not limited to, 3F8, abagovomab, adecatumumab, afutuzumab, alacizumab pegol, alemtuzumab (CAMPATH®, MABCAMPATH®), altumomab pentetate (HYBRI-CEAKER®), anatumomab mafenatox, anrukinzumab (IMA-638), apolizumab, arcitumomab (CEA-SCAN®), bavituximab, bectumomab (LYMPHOSCAN®), belimumab (BENLYSTA®, LYMPHOSTAT-B®), besilesomab (SCINTIMUN®), bevacizumab (AVASTIN®), bivatuzumab mertansine, blinatumomab, brentuximab vedotin, cantuzumab mertansine, capromab pendetide (PROSTASCINT®), catumaxomab (REMOVAB®), CC49, cetuximab (C225, ERBITUX®), citatuzumab bogatox, cixutumumab, clivatuzumab tetraxetan, conatumumab, dacetuzumab, denosumab (PROLIA®), detumomab, ecromeximab, edrecolomab (PANOREX®), elotuzumab, epitumomab cituxetan, epratuzumab, ertumaxomab (REXOMUN®), etaracizumab, farletuzumab, figitumumab, fresolimumab, galiximab, gemtuzumab ozogamicin (MYLOTARG®), girentuximab, glembatumumab vedotin, ibritumomab (ibritumomab tiuxetan, ZEVALIN®), igovomab (INDIMACIS-125®), intetumumab, inotuzumab ozogamicin, ipilimumab, iratumumab, labetuzumab (CEA-CIDE®), lexatumumab, lintuzumab, lucatumumab, lumiliximab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, nacolomab tafenatox, naptumomab estafenatox, necitumumab, nimotuzumab (THERACIM®, THERALOC®), nofetumomab merpentan (VERLUMA®), ofatumumab (ARZERRA®), olaratumab, oportuzumab monatox, oregovomab (OVAREX®), panitumumab (VECTIBIX®), pemtumomab (THERAGYN®), pertuzumab (OMNITARG®), pintumomab, pritumumab, ramucirumab, ranibizumab (LUCENTIS®), rilotumumab, rituximab (MABTHERA®, RITUXAN®), robatumumab, satumomab pendetide, sibrotuzumab, siltuximab, sontuzumab, tacatuzumab tetraxetan (AFP-CIDE®), taplitumomab paptox, tenatumomab, TGN1412, ticilimumab (tremelimumab), tigatuzumab, TNX-650, tositumomab (BEXXAR®), trastuzumab (HERCEPTIN®), tremelimumab, tucotuzumab celmoleukin, veltuzumab, volociximab, votumumab (HUMASPECT®), zalutumumab (HUMAX-EGFR®), and zanolimumab (HUMAX-CD4®).

In other embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in combination with a viral cancer therapeutic agent. Exemplary viral cancer therapeutic agents include, but not limited to, vaccinia virus (vvDD-CDSR), carcinoembryonic antigen-expressing measles virus, recombinant vaccinia virus (TK-deletion plus GM-CSF), Seneca Valley virus-001, Newcastle virus, coxsackie virus A21, GL-ONC1, EBNA1 C-terminal/LMP2 chimeric protein-expressing recombinant modified vaccinia Ankara vaccine, carcinoembryonic antigen-expressing measles virus, G207 oncolytic virus, modified vaccinia virus Ankara vaccine expressing p53,

OncoVEX GM-CSF modified herpes-simplex 1 virus, fowlpox virus vaccine vector, recombinant vaccinia prostate-specific antigen vaccine, human papillomavirus 16/18 L1 virus-like particle/AS04 vaccine, MVA-EBNA1/LMP2 Inj. vaccine, quadrivalent HPV vaccine, quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (GARDASIL®), recombinant fowlpox-CEA(6D)/TRICOM vaccine; recombinant vaccinia-CEA(6D)-TRICOM vaccine, recombinant modified vaccinia Ankara-5T4 vaccine, recombinant fowlpox-TRICOM vaccine, oncolytic herpes virus NV1020, HPV L1 VLP vaccine V504, human papillomavirus bivalent (types 16 and 18) vaccine (CERVARIX®), herpes simplex virus HF10, Ad5CMV-p53 gene, recombinant vaccinia DF3/MUC1 vaccine, recombinant vaccinia-MUC-1 vaccine, recombinant vaccinia-TRICOM vaccine, ALVAC MART-1 vaccine, replication-defective herpes simplex virus type I (HSV-1) vector expressing human Preproenkephalin (NP2), wild-type reovirus, reovirus type 3 Dearing (REOLYSIN®), oncolytic virus HSV1716, recombinant modified vaccinia Ankara (MVA)-based vaccine encoding Epstein-Barr virus target antigens, recombinant fowlpox-prostate specific antigen vaccine, recombinant vaccinia prostate-specific antigen vaccine, recombinant vaccinia-B7.1 vaccine, rAd-p53 gene, Ad5-delta24RGD, HPV vaccine 580299, JX-594 (thymidine kinase-deleted vaccinia virus plus GM-CSF), HPV-16/18 L1/AS04, fowlpox virus vaccine vector, vaccinia-tyrosinase vaccine, MEDI-517 HPV-16/18 VLP AS04 vaccine, adenoviral vector containing the thymidine kinase of herpes simplex virus TK99UN, HspE7, FP253/Fludarabine, ALVAC(2) melanoma multi-antigen therapeutic vaccine, ALVAC-hB7.1, canarypox-hIL-12 melanoma vaccine, Ad-REIC/Dkk-3, rAd-IFN SCH 721015, TIL-Ad-INFg, Ad-lSF35, and coxsackievirus A21 (CVA21, CAVATAK®).

In other embodiments, anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in combination with a nanopharmaceutical. Exemplary cancer nanopharmaceuticals include, but not limited to, ABRAXANE® (paclitaxel bound albumin nanoparticles), CRLX101 (CPT conjugated to a linear cyclodextrin-based polymer), CRLX288 (conjugating docetaxel to the biodegradable polymer poly (lactic-co-glycolic acid)), cytarabine liposomal (liposomal Ara-C, DEPOCYT™), daunorubicin liposomal (DAUNOXOME®), doxorubicin liposomal (DOXIL®, CAELYX®), encapsulated-daunorubicin citrate liposome (DAUNOXOME®), and PEG anti-VEGF aptamer (MACUGEN®).

In some embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in combination with paclitaxel or a paclitaxel formulation, e.g., TAXOL®, protein-bound paclitaxel (e.g., ABRAXANE®). Exemplary paclitaxel formulations include, but are not limited to, nanoparticle albumin-bound paclitaxel (ABRAXANE®, marketed by Abraxis Bioscience), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin, marketed by Protarga), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX, marketed by Cell Therapeutic), the tumor-activated prodrug (TAP), ANG105 (Angiopep-2 bound to three molecules of paclitaxel, marketed by ImmunoGen), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1; see Li et al., *Biopolymers* (2007) 87:225-230), and glucose-conjugated paclitaxel (e.g., 2'-paclitaxel methyl 2-glucopyranosyl succinate, see Liu et al., *Bioorganic & Medicinal Chemistry Letters* (2007) 17:617-620).

Exemplary RNAi and antisense RNA agents for treating cancer include, but not limited to, CALAA-01, siG12D LODER (Local Drug EluteR), and ALN-VSP02.

Other cancer therapeutic agents include, but not limited to, cytokines (e.g., aldesleukin (IL-2, Interleukin-2, PROLEUKIN®), alpha Interferon (IFN-alpha, Interferon alfa, INTRON® A (Interferon alfa-2b), ROFERON-A® (Interferon alfa-2a)), Epoetin alfa (PROCRIT®), filgrastim (G-CSF, Granulocyte-Colony Stimulating Factor, NEUPOGEN®), GM-CSF (Granulocyte Macrophage Colony Stimulating Factor, sargramostim, LEUKINE™), IL-11 (Interleukin-11, oprelvekin, NEUMEGA®), Interferon alfa-2b (PEG conjugate) (PEG interferon, PEG-INTRON™), and pegfilgrastim (NEULASTA™)), hormone therapy agents (e.g., aminoglutethimide (CYTADREN®), anastrozole (ARIMIDEX®), bicalutamide (CASODEX®), exemestane (AROMASIN®), fluoxymesterone (HALOTESTIN®), flutamide (EULEXIN®), fulvestrant (FASLODEX®), goserelin (ZOLADEX®), letrozole (FEMARA®), leuprolide (ELIGARD™, LUPRON®, LUPRON DEPOT®, VIADUR™), megestrol (megestrol acetate, MEGACE®), nilutamide (ANANDRON®, NILANDRON®), octreotide (octreotide acetate, SANDOSTATIN®, SANDOSTATIN LAR®), raloxifene (EVISTA®), romiplostim (NPLATE®), tamoxifen (NOVALDEX®), and toremifene (FARESTON®)), phospholipase A2 inhibitors (e.g., anagrelide (AGRYLIN®)), biologic response modifiers (e.g., BCG (THERACYS®, TICE®), and Darbepoetin alfa (ARANESP®)), target therapy agents (e.g., bortezomib (VELCADE®), dasatinib (SPRYCEL™), denileukin diftitox (ONTAK®), erlotinib (TARCEVA®), everolimus (AFINITOR®), gefitinib (IRESSA®), imatinib mesylate (STI-571, GLEEVEC™), lapatinib (TYKERB®), sorafenib (NEXAVAR®), and SU11248 (sunitinib, SUTENT®)), immunomodulatory and antiangiogenic agents (e.g., CC-5013 (lenalidomide, REVLIMID®), and thalidomide (THALOMID®)), glucocorticosteroids (e.g., cortisone (hydrocortisone, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, ALA-CORT®, HYDROCORT ACETATE®, hydrocortone phosphate LANACORT®, SOLU-CORTEF®), decadron (dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, DEXASONE®, DIODEX®, HEXADROL®, MAXIDEX®), methylprednisolone (6-methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, DURALONE®, MEDRALONE®, MEDROL®, M-PREDNISOL®, SOLU-MEDROL®), prednisolone (DELTA-CORTEF®, ORAPRED®, PEDIAPRED®, PRELONE®), and prednisone (DELTASONE®, LIQUID PRED®, METICORTEN®, ORASONE®)), and bisphosphonates (e.g., pamidronate (AREDIA®), and zoledronic acid (ZOMETA®))

In some embodiments, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is used in combination with a tyrosine kinase inhibitor (e.g., a receptor tyrosine kinase (RTK) inhibitor). Exemplary tyrosine kinase inhibitor include, but are not limited to, an epidermal growth factor (EGF) pathway inhibitor (e.g., an epidermal growth factor receptor (EGFR) inhibitor), a vascular endothelial growth factor (VEGF) pathway inhibitor (e.g., an antibody against VEGF, a VEGF trap, a vascular endothelial growth factor receptor (VEGFR) inhibitor (e.g., a VEGFR-1 inhibitor, a VEGFR-2 inhibitor, a VEGFR-3 inhibitor)), a platelet derived growth factor (PDGF) pathway inhibitor (e.g., a platelet derived growth factor receptor (PDGFR) inhibitor (e.g., a PDGFR-β inhibitor)), a RAF-1 inhibitor, a KIT inhibitor and a RET inhibitor. In some embodiments, the

anti-cancer agent used in combination with the AHCM agent is selected from the group consisting of: axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib ORES SA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BMW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIM 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, XL228, AEE788, AG-490, AST-6, BMS-599626, CUDC-101, PD153035, pelitinib (EKB-569), vandetanib (zactima), WZ3146, WZ4002, WZ8040, ABT-869 (linifanib), AEE788, AP24534 (ponatinib), AV-951 (tivozanib), axitinib, BAY 73-4506 (regorafenib), brivanib alaninate (BMS-582664), brivanib (BMS-540215), cediranib (AZD2171), CHIR-258 (dovitinib), CP 673451, CYC116, E7080, Ki8751, masitinib (AB1010), MGCD-265, motesanib diphosphate (AMG-706), MP-470, OSI-930, Pazopanib Hydrochloride, PD173074, Sorafenib Tosylate (Bay 43-9006), SU 5402, TSU-68 (SU6668), vatalanib, XL880 (GSK1363089, EXEL-2880). Selected tyrosine kinase inhibitors are chosen from sunitinib, erlotinib, gefitinib, or sorafenib. In one embodiment, the tyrosine kinase inhibitor is sunitinib.

In one embodiment, the anti-TCRβV antibody molecule, multispecific or multifunctional molecule is administered in combination with one of more of: an anti-angiogenic agent, or a vascular targeting agent or a vascular disrupting agent. Exemplary anti-angiogenic agents include, but are not limited to, VEGF inhibitors (e.g., anti-VEGF antibodies (e.g., bevacizumab); VEGF receptor inhibitors (e.g., itraconazole); inhibitors of cell proliferatin and/or migration of endothelial cells (e.g., carboxyamidotriazole, TNP-470); inhibitors of angiogenesis stimulators (e.g., suramin), among others. A vascular-targeting agent (VTA) or vascular disrupting agent (VDA) is designed to damage the vasculature (blood vessels) of cancer tumors causing central necrosis (reviewed in, e.g., Thorpe, P. E. (2004) *Clin. Cancer Res. Vol.* 10:415-427). VTAs can be small-molecule. Exemplary small-molecule VTAs include, but are not limited to, microtubule destabilizing drugs (e.g., combretastatin A-4 disodium phosphate (CA4P), ZD6126, AVE8062, Oxi 4503); and vadimezan (ASA404).

Immune Checkpoint Inhibitors

In other embodiments, methods described herein comprise use of an immune checkpoint inhibitor in combination with the anti-TCRβV antibody molecule, multispecific or multifunctional molecule. The methods can be used in a therapeutic protocol in vivo.

In embodiments, an immune checkpoint inhibitor inhibits a checkpoint molecule. Exemplary checkpoint molecules include but are not limited to CTLA4, PD1, PD-L1, PD-L2, TIM3, LAG3, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), BTLA, KIR, MHC class I, MHC class II, GALS, VISTA, BTLA, TIGIT, LAIR1, and A2aR. See, e.g., Pardoll. Nat. Rev. Cancer 12.4(2012):252-64, incorporated herein by reference.

In embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor, e.g., an anti-PD-1 antibody such as Nivolumab, Pembrolizumab or Pidilizumab. Nivolumab (also called MDX-1106, MDX-1106-04, ONO-4538, or BMS-936558) is a fully human IgG4 monoclonal antibody that specifically inhibits PD1. See, e.g., U.S. Pat. No. 8,008,449 and WO2006/121168. Pembrolizumab (also called Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA®; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. See, e.g., Hamid, O. et al. (2013) *New England Journal of Medicine* 369 (2): 134-44, U.S. Pat. No. 8,354,509 and WO2009/114335. Pidilizumab (also called CT-011 or Cure Tech) is a humanized IgG1k monoclonal antibody that binds to PD1. See, e.g., WO2009/101611. In one embodiment, the inhibitor of PD-1 is an antibody molecule having a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence of Nivolumab, Pembrolizumab or Pidilizumab. Additional anti-PD1 antibodies, e.g., AMP 514 (Amplimmune), are described, e.g., in U.S. Pat. No. 8,609,089, US 2010028330, and/or US 20120114649.

In some embodiments, the PD-1 inhibitor is an immunoadhesin, e.g., an immunoadhesin comprising an extracellular/PD-1 binding portion of a PD-1 ligand (e.g., PD-L1 or PD-L2) that is fused to a constant region (e.g., an Fc region of an immunoglobulin). In embodiments, the PD-1 inhibitor is AMP-224 (B7-DCIg, e.g., described in WO2011/066342 and WO2010/027827), a PD-L2 Fc fusion soluble receptor that blocks the interaction between B7-H1 and PD-1.

In embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor, e.g., an antibody molecule. In some embodiments, the PD-L1 inhibitor is YW243.55.570, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105. In some embodiments, the anti-PD-L1 antibody is MSB0010718C (also called A09-246-2; Merck Serono), which is a monoclonal antibody that binds to PD-L1. Exemplary humanized anti-PD-L1 antibodies are described, e.g., in WO2013/079174. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody, e.g., YW243.55.S70. The YW243.55.S70 antibody is described, e.g., in WO 2010/077634. In one embodiment, the PD-L1 inhibitor is MDX-1105 (also called BMS-936559), which is described, e.g., in WO2007/005874. In one embodiment, the PD-L1 inhibitor is MDPL3280A (Genentech/Roche), which is a human Fc-optimized IgG1 monoclonal antibody against PD-L1. See, e.g., U.S. Pat. No. 7,943,743 and U.S Publication No.: 20120039906. In one embodiment, the inhibitor of PD-L1 is an antibody molecule having a sequence substantially identical or similar thereto, e.g., a sequence at least 85%, 90%, 95% identical or higher to the sequence of YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1105.

In embodiments, the immune checkpoint inhibitor is a PD-L2 inhibitor, e.g., AMP-224 (which is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD1 and B7-H1. See, e.g., WO2010/027827 and WO2011/066342.

In one embodiment, the immune checkpoint inhibitor is a LAG-3 inhibitor, e.g., an anti LAG-3 antibody molecule. In embodiments, the anti-LAG-3 antibody is BMS-986016 (also called BMS986016; Bristol-Myers Squibb). BMS-986016 and other humanized anti-LAG-3 antibodies are described, e.g., in US 2011/0150892, WO2010/019570, and WO2014/008218.

In embodiments, the immune checkpoint inhibitor is a TIM-3 inhibitor, e.g., anti-TIM3 antibody molecule, e.g., described in U.S. Pat. No. 8,552,156, WO 2011/155607, EP 2581113 and U.S Publication No.: 2014/044728.

In embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, e.g., anti-CTLA-4 antibody molecule. Exemplary anti-CTLA4 antibodies include Tremelimumab (IgG2 monoclonal antibody from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (also called MDX-010, CAS No. 477202-00-9). Other exemplary anti-CTLA-4 antibodies are described, e.g., in U.S. Pat. No. 5,811,097.

CRS Grading

In some embodiments, CRS can be graded in severity from 1-5 as follows. Grades 1-3 are less than severe CRS. Grades 4-5 are severe CRS. For Grade 1 CRS, only symptomatic treatment is needed (e.g., nausea, fever, fatigue, myalgias, malaise, headache) and symptoms are not life threatening. For Grade 2 CRS, the symptoms require moderate intervention and generally respond to moderate intervention. Subjects having Grade 2 CRS develop hypotension that is responsive to either fluids or one low-dose vasopressor; or they develop grade 2 organ toxicity or mild respiratory symptoms that are responsive to low flow oxygen (<40% oxygen). In Grade 3 CRS subjects, hypotension generally cannot be reversed by fluid therapy or one low-dose vasopressor. These subjects generally require more than low flow oxygen and have grade 3 organ toxicity (e.g., renal or cardiac dysfunction or coagulopathy) and/or grade 4 transaminitis. Grade 3 CRS subjects require more aggressive intervention, e.g., oxygen of 40% or higher, high dose vasopressor(s), and/or multiple vasopressors. Grade 4 CRS subjects suffer from immediately life-threatening symptoms, including grade 4 organ toxicity or a need for mechanical ventilation. Grade 4 CRS subjects generally do not have transaminitis. In Grade 5 CRS subjects, the toxicity causes death. Sets of criteria for grading CRS are provided herein as Table 5, Table 6, and Table 7. Unless otherwise specified, CRS as used herein refers to CRS according to the criteria of Table 6.

In embodiments, CRS is graded according to Table 5:

TABLE 5

CRS grading	
Gr1	Supportive care only
Gr2	IV therapies +/− hospitalization.
Gr3	Hypotension requiring IV fluids or low-dose vasoactives or hypoxemia requiring oxygen, CPAP, or BIPAP.
Gr4	Hypotension requiring high-dose vasoactives or hypoxemia requiring mechanical ventilation.
Gr 5	Death

TABLE 6

CTCAE v 4.0 CRS grading scale	
CRS grade	Characteristics
Grade 1	Mild; No infusion interruption; No intervention
Grade 2	Infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs
Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4	Life threatening consequences; pressor or ventilator support

TABLE 7

NCI CRS grading scale	
CRS grade	Characteristics
Grade 1	Symptoms are not life threatening and require symptomatic treatment only; e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention; Oxygen requirement <40% or hypotension responsive to fluids or low dose pressors or Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention; Oxygen requirement >=40% or Hypotension requiring high dose or multiple pressors or grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life threatening symptoms Requirement for ventilator support or Grade 4; organ toxicity (excluding transaminitis)

EXAMPLES

Example 1. Humanization of α-TRBV6-5 Antibody Clone Antibody A

The germline for the mouse α-TCRβ antibody clone Antibody A VH and VL were assigned using IMGT nomenclature, with CDR regions defined by a combined Kabat and Chothia classification. SEQ ID NO: 1 and SEQ ID NO: 2 are the Antibody A VH and VL sequences respectively where the VH germline is mouse IGHV1S12*01 and the VL germline is mouse IGKV6-15*01. SEQ ID NOs: 3-5 are the Antibody A VH CDR regions 1-3 respectively and SEQ ID NOs: 6-8 correspond to the VL CDR regions 1-3 (as described in Table 1).

Humanization of the Antibody A VH and VL sequences was done separately using similar methodology. Amino acids positions were identified in the framework regions which were important for the success of CDR grafting. Human germline sequences were identified which preserved the necessary residues and contained a high amount of overall identity. When the human germline framework sequence did not contain a matching important amino acid, it was back mutated to match the mouse sequence. CDR regions were grafted onto the human germline unchanged. The Antibody A VH was humanized into human IGHV1-69*01 and the Antibody A VL was humanized into IGKV1-17*01 and IGKV1-27*01. All 3 humanized sequences were confirmed to contain no introduced potential negative post translational modification sites such as NG, DG, NS, NN, DS, NT, NXS, or NXT as a result of the humanization process. SEQ ID NO: 9 is the humanized Antibody A-H.1 VH and SEQ ID NOs: 10 and 11 are the humanized VL IGKV1-17*01 and IGKV1-27*01 germlines respectively (as described in Table 1). FIGS. **1**A and **1**B show the murine and humanized sequences with annotations depicting the CDR and framework regions (FR).

Example 2: Humanization of α-TRBV12-3 and TRBV12-4 Antibody Clone Antibody B

The germline for the mouse α-TCRβ antibody clone Antibody B VH and VL were assigned using IMGT nomenclature, with CDR regions defined by a combined Kabat and Chothia classification. SEQ ID NO: 15 and SEQ ID NO: 16 are the Antibody B VH and VL sequences respectively where the VH germline is mouse IGHV5-17*02 and the VL germline is mouse IGKV4-50*01. SEQ ID NOs: 17-19 are the B-H VH CDR regions 1-3 respectively and SEQ ID NOs: 20-22 are the B-H VL CDR regions 1-3 (as described in Table 2).

The method applied to humanize Antibody A described in Example 1 was used to humanize Antibody B. The Antibody B VH was humanized into human IGHV3-30*01, IGHV3-48*01, and IGHV3-66*01 and the Antibody B VL was humanized into human IGKV1-9*01, IGKV1-39*01, IGKV3-15*01, IGLV1-47*01 and IGLV3-10*01. SEQ ID NOs: 23-25 are the B-H.1A, B-H.1B, and B-H.1C humanized heavy chains and SEQ ID NOs: 26-30 are the B-H.1D, B-H.1E, B-H.1F, B-H.1G and B-H.1H humanized light chains (as described in Table 2). FIGS. **2**A and **2**B show the murine and humanized sequences with annotations depicting the CDR and framework regions (FR).

Example 3: Characteristics of Anti-TCRβV Antibodies

Introduction

Current bispecific constructs designed to redirect T cells to promote tumor cell lysis for cancer immunotherapy typically utilize single chain variable fragments (scFVs) that are derived from monoclonal antibodies (mAb) directed against the CD3e subunit of the T cell receptor (TCR). However, there are limitations to this approach which may prevent the full realization of the therapeutic potential for such bispecific constructs. Previous studies have shown that, e.g., low "activating" doses of anti-CD3e mAb can cause long-term T cell dysfunction and exert immunosuppressive effects. In addition, anti-CD3e mAbs bind to all T cells and thus activate equally all T cells, which has been associated with the first dose side effects of anti-CD3e mAbs that result from massive T cell activation. These large number of activated T cells secrete substantial amounts of cytokines, the most important of which is Interferon gamma (IFNg). This excess amount of IFNg in turn, e.g., activates macrophages which then can overproduce proinflammatory cytokines such as IL-1, IL-6 and TNF-alpha, causing a "cytokine storm" known as the cytokine release syndrome (CRS). Thus, it might be advantageous to develop antibodies that are capable of binding and activating only a subset of necessary effector T cells to reduce the CRS.

Results

To that end, antibodies directed to the variable chain of the beta subunit of TCR (TCR Vb) were identified. These anti-TCR Vb antibodies bind and activate a subset of T cells, but with, e.g., no or markedly reduced CRS. Using plate-bound anti-TCR Vb13.1 mAbs (A-H.1 and A-H.2) it was shown that a population of T cells, defined by positive staining with A-H.1, can be expanded (from ~5% of T cells on day 0 to almost 60% of total T cells on day 6 of cell culture) (FIGS. **4**A-**4**C). For this experiment, human CD3+ T cells were isolated using magnetic-bead separation (negative selection) and activated with immobilized (plate-coated) A-H.1 or OKT3 (anti-CD3e) antibodies at 100 nM for 6 days. The expanded Vb13.1+ T cells display cytolytic activity against transformed cell line RPMI-8226 when co-cultured with purified CD3+ T cells (FIGS. **5**A-**5**B).

Next, the ability of PBMCs activated by anti-TCR VB antibodies to produce cytokines was assessed. The cytokine production of PBMCs activated with anti-TCR VB antibodies was compared to the cytokine production of PBMCs activated with: (i) anti-CD3e antibodies (OKT3 or SP34-2); (ii) anti-TCR V alpha (TCR VA) antibodies including anti-TCR VA 12.1 antibody 6D6.6, anti-TCR VA24JA18 antibody 6B11; (iii) anti-TCR alpha beta antibody T10B9; and/or (iv) isotype control (BGM0109). The anti-TCR VB antibodies tested include: humanized anti-TCRVB 13.1 antibodies (A-H.1, or A-H.2), murine anti-TCR VB5 antibody Antibody E, murine anti-TCR VB8.1 antibody Antibody B, and murine anti-TCR VB12 antibody Antibody D. BGM0109 comprises the amino acid sequence of METDTLLLWVLLLWVPGSTGGLNDIFEAQK-IEWHEGGGGSEPRTDTDTCPNPPDPCPTC PTPDLLGGPSVFIFPPKPKDVLMISLTPKITCVVVDV-SEEEPDVQFNWYVNNVEDKTAQT ETRQRQYN-STYRVVSVLPIKHQDWMSGKVFKCKVNN-NALPSPIEKTISKPRGQVRVPQI YTFPPPIEQTVKKDVSVTCLVTGFLPQ-DIHVEWESNGQPQPEQNYKNTQPVLDSDGSYFL YSKLNVPKSRWDQGDSFTCSVIHEALHNHHMTKTIS-RSLGNGGGGS (SEQ ID NO: 3282).

As shown in FIG. **6**A, when plate-bound A-H.1 or A-H.2, or anti-CD3e antibodies (OKT3 or SP34-2) were used to activate human PBMCs, the T cell cytokine IFNg was induced (FIG. **6**A). All anti-TCR VB antibodies tested had a similar effect on the production of IFNg (FIG. **6**B). The anti-TCR VA antibodies did not induce similar IFNg production.

With respect to IL-2 production, PBMCs activated with A-H.1 and A-H.2 resulted in increased IL-2 production (FIG. **7**A) with delayed kinetics (FIG. **7**B) as compared to PBMCs activated with anti-CD3e antibodies (OKT3 or SP34-2). FIG. **7**B shows that anti-TCR VB antibody activated PBMCs demonstrate peak production of IL-2 at Day 5 or Day 6 post-activation (incubation with plate-coated antibodies). In contrast, IL-2 production in PBMCs activated with OKT3 peaked at day 2 post-activation. As with IFNG, the IL-2 effect (e.g., enhanced production of IL-2 and delayed kinetics) was similar across all anti-TCR VB antibodies tested (FIG. **7**B).

The production of cytokines IL-6, IL-1β and TNF-alpha which are associated with "cytokine storms" (and accordingly CRS) was also assessed under similar conditions. FIGS. **8**A, **9**A and **10**A shows that while PBMCs activated with anti-CD3e antibodies demonstrate production of IL-6 (FIG. **8**A), TNF-alpha (FIG. **9**A) and IL-1β (FIG. **10**A), no or little induction of these cytokines was observed with PBMCs activated with A-H.1 or A-H.2. As shown in FIGS. **9**B and **10**B, TNF-alpha and IL-1β production was not induced by activation of PBMCs with any of the anti-TCR VB antibodies.

It was further noted that the kinetics of IFNg production by A-H.1-activated CD3+ T cells was delayed relative to those produced by CD3+ T cells activated by anti-CD3e mAbs (OKT3 and SP34-2) (FIGS. **11**A and **11**B).

Finally, it was observed that the subset of memory effector T cells known as T_{EMRA} was preferentially expanded in CD8+ T cells activated by A-H.1 or A-H.2 (FIG. **12**). Isolated human PBMCs were activated with immobilized (plate-coated) anti-CD3e or anti-TCR Vβ13.1 at 100 nM for 6-days. After a 6-day incubation, T-cell subsets were identified by FACS staining for surface markers for Naive T cell

(CD8+, CD95−, CD45RA+, CCR7+), T stem cell memory (TSCM; CD8+, CD95+, CD45RA+, CCR7+), T central memory (Tcm; CD8+, CD95+, CD45RA−, CCR7+), T effector memory (Tem; CD8+, CD95+, CD45RA−, CCR7−), and T effector memory re-expressing CD45RA (Temra; CD8+, CD95+, CD45RA+, CCR7−). Human PBMCs activated by anti-TCR Vβ13.1 antibodies (A-H.1 or A-H.2) increased CD8+ TSCM and Temra T cell subsets when compared to PBMCs activated by anti-CD3e antibodies (OKT3 or SP34-2). Similar expansion was observed with CD4+ T cells.

Conclusion

The data provided in this Example show that antibodies directed against TCR Vb can, e.g., preferentially activate a subset of T cells, leading to an expansion of T_{EMRA}, which can, e.g., promote tumor cell lysis but not CRS. Thus, bispecific constructs utilizing either a Fab or scFV or a peptide directed to the TCR Vb can, e.g., be used to activate and redirect T cells to promote tumor cell lysis for cancer immunotherapy, without, e.g., the harmful side-effects of CRS associated with anti-CD3e targeting.

Example 4: On-Target T Cell Mediated Cytotoxicity of Multiple Myeloma (MM) Cells with a Dual-Targeting Antibody Molecule Against BCMA and a T Cell Engager

This example shows on-target T cell mediated cytotoxicity of multiple myeloma (MAUI) cells with dual-targeting antibody molecules that recognize a T cell engager, e.g., TCRVb, on T cells and BCMA on MM cells.

As shown in FIG. **13**A, purified human T cells activated with plate-bound anti-TCRVb antibody for 5 days proliferate at a higher rate than purified human T cells activated with plate-bound anti-CD3 (OKT3) antibody. Anti-TCRVb antibody stimulation of T cells resulted in selective expansion of CD45RA+ effector memory CD8+ and CD4+ T cells (TEMRA) cells (FIG. **13**B). Both CD8+ and CD4+ Temra cell populations expanded more when stimulated with an anti-TCRVb antibody, compared to unstimulated cells or cells stimulated with an anti-CD3 (SP34) antibody. Anti-TCRVb antibodies resulted in delayed secretion of IFN-g by PBMCs stimulated with an anti-TCRVb antibody compared to PBMCs stimulated with anti-CD3 antibodies (FIG. **13**C). Additionally, T cells stimulated with anti-TCRVb antibody or anti-CD3 antibodies resulted in comparable lysis of multiple myeloma target cells, as shown in FIG. **13**D. As shown in FIGS. **13**E-**13**F, T cells stimulated for 5 days with 100 ng/ml plate-bound an anti-TCRVb antibody, or an anti-CD3 antibody secreted perforin and Granzyme B.

Activation of PBMCs with anti-TCRVb antibody resulted in higher production and/or secretion of IL-2 and/or IL-15 compared to PBMCs activated with an anti-OKT3 antibody (FIG. **14**A). Anti-TCRVb antibody activated of PBMCs also resulted in expansion and/or survival, e.g., proliferation of Natural Killer (NK) cells (FIG. **14**B). In comparison, PBMCS activated with an anti-OKT3 antibody did not result in NK cell expansion. Further, as described in Example 3, PBMCs activated with an anti-TCRVb antibody did not result in the production of cytokines IL-6, IL-1β and TNF-alpha which are associated with CRS (FIG. **15**). These in vitro characterization studies show that in some embodiments, anti-TCRVb antibodies, e.g., activate and/or stimulate, T cells to promote T cell killing as evidenced by target cell lysis, perforin secretion and granzyme B secretion, and secretion of IFN-g with, e.g., delayed kinetics.

Next, the ability of a dual-targeting antibody molecule (Molecule I), which targets BCMA on one arm and TCRVb on the other arm, to target and kill multiple myeloma (MM) cells was tested. Healthy donor PBMCs were co-incubated with the RMPI8226 MM cell line and one of the following dual-targeting antibody molecules: BCMA-TCRVb (Molecule I), BCMA-CD3, or Control-TCRVb; or an isotype control Target cell lysis was then assessed using flow cytometry. As shown in FIG. **16**A, the dual-targeting BCMA-TCRVb antibody molecule (Molecule I) resulted in killing of MM cells in vitro.

The dual-targeting BCMA-TCRVb antibody molecule (Molecule I) was further tested in vivo for its ability to inhibit MM tumor growth in a MM mouse model. The NCI-H929 cell line was injected in NOD-scid IL2rγnull (NSG)recipient mice on Day 0 followed by delivery of PBMCs on Day 9. On Days 12, 15, 18 and 21, the dual-targeting BCMA-TCRVb antibody molecule (Molecule I) was administered via intraperitoneal injection at a dose of 0.5 mg/kg. FIG. **16**B shows prevention, e.g., inhibition, of MM tumor growth in vivo with the dual-targeting BCMA-TCRVb antibody molecule (Molecule I). These results demonstrate that in some embodiments the dual-targeting BCMA-TCRVb antibody molecule, e.g., can kill tumor cells, e.g., MM tumor cells, in vitro and in vivo. Accordingly, in some embodiments, a dual-targeting BCMA-TCRVb antibody molecule can be used, e.g., as a therapy for cancer, e.g., a hematological cancer, e.g., MM.

Example 5: In Vitro Cytotoxicity of a Dual-Targeting Antibody Molecule Against FcRH5 and a T Cell Engager

This example shows in vitro cytotoxicity on multiple myeloma (MM) cells with a dual-targeting antibody molecule that recognizes a T cell engager, e.g., TCRVb, on T cells and FcRH5 on MM cells. Healthy donor PBMCs or purified T cells were co-incubated with the MOL8M MM cell line and a dual-targeting antibody molecule which targets FcRH5 on one arm and TCRVb on the other arm (Molecule E), or with an isotype control antibody. Target cell lysis was then assessed using flow cytometry. As shown in FIG. **17**, the dual targeting FcRH5-TCRVb molecule (Molecule E) resulted in killing of MM cells by both purified T cells or PBMCs. This shows that the dual targeting FcRH5-TCRVb molecule can target and promote killing of MM cells by immune cells, e.g., in PBMCs, including T cells.

Example 6: Characteristics of Anti-TCR Vβ8a Antibodies

This Example shows in vitro characterization of anti-TCR Vβ8a antibodies (B-H.1). TCR Vβ8 is also referred to as TCR Vβ12 (as described in Table 8). Isolated human PBMCs were activated with immobilized (plate-coated) anti-CD3∈ or anti-TCR Vβ8a at 100 nM, and cell culture supernatants were collected on day 1, 2, 3, 5, 6 and 8 post stimulation. Cytokines (IFNγ, IL-2, TNFα, IL-1β or IL-6) were measured using MSD technology platform (MesoScale Discovery) as described in the manufacturer's protocol.

As shown in FIGS. **18**A-**18**B, Human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) produce similar or reduced levels of IFNγ (FIG. **18**A) and higher levels IL-2 (FIG. **18**B) when compared to those activated by anti-CD3∈ antibodies (OKT3 or SP34-2).

FIGS. **19**A-**19**B show that human PBMCs activated by anti-TCR Vβ8a antibodies (B-H.1) do not produce significant levels of IL-6, or IL1b. Activation of human PBMCs with anti-TCR Vβ8a antibodies (B-H.1) also results in lesser TNFa when compared to PBMCs activated by anti-CD3∈ antibodies (OKT3 or SP34-2) (see FIG. **19**C).

In summary, as shown in Example 3, this Example shows that anti-TCR Vβ8a antibodies can, e.g., preferentially induce expression of T cell cytokines, e.g., IL-2 and IFNg, but not production of cytokines IL-6, IL-1β and TNF-alpha which are associated with "cytokine storms" (and accordingly CRS).

Example 7: Characteristics of Anti-TCRβV Antibody D Antibody

This Example describes characterization of anti-TCRβV antibodies which can bind and activate a subset of T cells, but with, e.g., no or markedly reduced, CRS.

Human PBMCs were isolated from whole blood followed by solid-phase (plate-coated) stimulation with anti-TCR Vβ12 antibody (Antibody D) or anti-CD3e antibodies (OKT3) at 100 nM. Supernatant was collected on Days 1, 2, 3, 5, or 6 followed by multiplex cytokine analysis for IFNg, IL-2, IL-6, IL-1beta, or TNFalpha. The data was quantified using MSD (Meso Scale Discovery) platform, following the manufacturer's protocol.

As shown in FIG. **20**A, when plate-bound anti-TCR Vβ12 antibody (Antibody D) or anti-CD3e antibodies (OKT3) were used to activate human PBMCs, the T cell cytokine IFNg was induced. With respect to IL-2 production, PBMCs activated with anti-TCR Vβ12 antibody (Antibody D) resulted in increased IL-2 production with delayed kinetics (FIG. **20**B) as compared to PBMCs activated with anti-CD3e antibodies (OKT3).

The production of cytokines IL-6, IL-1β and TNF-alpha which are associated with "cytokine storms" (and accordingly CRS) was also assessed under similar conditions. FIGS. **20**C-**20**E show that that while PBMCs activated with anti-CD3e antibodies demonstrate production of IL-6 (FIG. **20**D), TNF-alpha (FIG. **20**C) and IL-1β (FIG. **20**E), no or little induction of these cytokines was observed with PBMCs activated with anti-TCR Vβ12 antibody (Antibody D).

The data provided in this Example show that antibodies directed against TCR Vβ can, e.g., preferentially activate a subset of T cells, and do not results in induction of cytokines associated with cytokine storms or CRS.

Example 8: Characteristics of Anti-TCRβV Antibody E

This Example describes characterization of anti-TCRβV antibodies which can bind and activate a subset of T cells, but with, e.g., no or markedly reduced, CRS.

Human PBMCs were isolated from whole blood followed by solid-phase (plate-coated) stimulation with anti-TCR Vβ5 antibody (Antibody E) or anti-CD3e antibodies (OKT3 and SP34-2), each at 100 nM. Supernatant was collected on Days 1, 3, 5, or 7 followed by multiplex cytokine analysis for IFNg, IL-2, IL-6, IL-1beta, IL-10 or TNFalpha. The data was quantified using MSD (Meso Scale Discovery) platform, following the manufacturer's protocol.

As shown in FIG. **21**A, when plate-bound anti-TCR Vβ5 antibody (Antibody E) or anti-CD3e antibodies (OKT3 and SP34-2) were used to activate human PBMCs, the T cell cytokine IFNg was induced. With respect to IL-2 production, PBMCs activated with anti-TCR Vβ5 antibody (Antibody E) resulted in increased IL-2 production with delayed kinetics (FIG. **21**B) as compared to PBMCs activated with anti-CD3e antibodies (OKT3 or SP34-2).

The production of cytokines IL-6, IL-13, IL-10 and TNF-alpha which are associated with "cytokine storms" (and accordingly CRS) was also assessed under similar conditions. FIGS. **22**A-**22**D show that that while PBMCs activated with anti-CD3e antibodies demonstrate production of IL-1β, (FIG. **22**A), IL-6 (FIG. **22**B), TNF-alpha (FIG. **22**C) and IL-10 (FIG. **22**D), no or little induction of these cytokines was observed with PBMCs activated with anti-TCR Vβ5 antibody (Antibody E).

The data provided in this Example show that antibodies directed against TCR Vβ, can, e.g., preferentially activate a subset of T cells, and do not results in induction of cytokines associated with cytokine storms or CRS.

Example 9: Characteristics of a Dual-Targeting Antibody Molecule Against BCMA and TCRβV

This Example describes characterization of a dual targeting antibody (e.g., a bispecific molecule) comprising an anti-TCRβV binding moiety and a BCMA binding moiety (Molecule H) which can bind and activate a subset of T cells, but with, e.g., no or markedly reduced, CRS.

Human PBMCs were isolated from whole blood followed by solid-phase (plate-coated) stimulation with an anti-TCRβV x BCMA bispecific molecule (Molecule H) or anti-CD3e antibodies (OKT3), each at 100 nM. Supernatant was collected on Days 1, 2, 3, or 5 followed by multiplex cytokine analysis for IFNg, IL-2, IL-6, IL-1beta, IL-10 or TNFalpha. The data was quantified using MSD (Meso Scale Discovery) platform, following the manufacturer's protocol.

As shown in FIG. **23**A, when plate-bound anti-TCRβV x BCMA bispecific molecule (Molecule H) or anti-CD3e antibodies (OKT3) were used to activate human PBMCs, the T cell cytokine IFNg was induced. With respect to IL-2 production, PBMCs activated with anti-TCRβV x BCMA bispecific molecule (Molecule H) resulted in increased IL-2 production (FIG. **23**B) as compared to PBMCs activated with anti-CD3e antibodies (OKT3).

The production of cytokines IL-6, IL-1β, IL-10 and TNF-alpha which are associated with "cytokine storms" (and accordingly CRS) was also assessed under similar conditions. FIGS. **23**C-E show that that while PBMCs activated with anti-CD3e antibodies demonstrate production of IL-1β (FIG. **23**C), IL-6 (FIG. **23**D), TNF-alpha (FIG. **23**D) and IL-10 (FIG. **23**E), no or little induction of these cytokines was observed with PBMCs activated with anti-TCRβV x BCMA bispecific molecule (Molecule H).

The data provided in this Example show that antibodies directed against TCR Vβ can, e.g., preferentially activate a subset of T cells, and do not result in induction of cytokines associated with cytokine storm or CRS.

Example 10: Cytokine and Chemokine Profile of Anti-TCRVb Antibodies

This Examples describes cytokines and chemokines secreted by PBMCs following activation by anti-TCR Vβ antibodies.

Human PBMCs were isolated from whole blood followed by solid-phase (plate-coated) stimulation with an anti-TCRβV antibodies (A-H.1, B-H.1), or a bispecific molecule comprising an anti-TCRVb antibody (Molecule H), an isotype control (BGM0122) or an anti-CD3e antibody (SP34),

each at 100 nM. Supernatant was collected on Days 1, 2, 3, 4, 5, 6, 7 and 8 followed by multiplex analysis for the indicated cytokines or chemokines. The data was quantified using MSD (Meso Scale Discovery) platform, following the manufacturer's protocol. BGM0122 comprises the amino acid sequence of METDTLLLWVLLLWVPGSTGDKTH-TCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE-EQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKA-LPAPIEKTISKAKGQPREPQVYTLPPSREEMT-KNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK-LTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSL-SPGKGGGGSGGGGSGLNDIFEAQKIEWHE (SEQ ID NO: 3283).

FIGS. **25**A-**25**J, FIGS. **26**A-**26**H, and FIGS. **27**A-**27**L show the levels of cytokine and chemokine from PBMCs activated with the indicated antibodies.

As shown in FIG. **25**A, when plate-bound anti-TCR Vβ antibodies or anti-CD3e antibodies (OKT3) were used to activate human PBMCs, the T cell cytokine IFNg was induced. With respect to IL-2 production, PBMCs activated with anti-TCR Vβ antibodies resulted in increased IL-2 production with delayed kinetics (FIG. **25**B) as compared to PBMCs activated with anti-CD3e antibody (OKT3).

While IL-1beta (FIG. **25**C), IL-6 (FIG. **25**D), IL-10 (FIG. **25**E), IL-4 (FIG. **25**F), TNFalpha (FIG. **25**G), IP-10 (FIG. **26**C), IL-12-23p40 (FIG. **27**D), IL-17A (FIG. **27**G), and IL-1a (FIG. **27**H), were induced by anti-CD3e antibody (OKT3), no or little induction of these cytokines or chemokines was observed with PBMCs activated with anti-TCRVb antibodies.

PBMCs activated with anti-TCR Vβ antibodies demonstrated induction of IL-13 (FIG. **251**), IL-8 (FIG. **25**J), Eotaxin (FIG. **26**A), Eotaxin 3 (FIG. **26**B), IL-18 (HA) (FIG. **26**C), MCP-1 (FIG. **26**E), MCP-4 (FIG. **26**F), MDC (FIG. **26**G), MIP1a (FIG. **2611**), MIP1B (FIG. **27**A), TARC (FIG. **27**B), GM-CSF (FIG. **27**C), IL-15 (FIG. **27**E), IL-16 (FIG. **27**F), and IL-15 (FIG. **27**I), IL-7 (FIG. **27**J).

Example 11: Nanostring-Based Gene Expression Profiling of TCR Vb-Activated T Cells

This Example describes gene expression profiling of TCR Vβ-activated T cells to, e.g., uncover potential mechanisms or pathways underlying TCR Vβ activation of T cells.

In a first study, the anti-TCR Vβ13.1 antibody A-H.1 was compared with an anti-CD3 antibody OKT3. Briefly, human PBMCs were isolated from whole blood. From isolated PBMCs, human CD3+ T cells were isolated using magnetic-bead separation (negative selection) (Miltenyi biotec) and activated by immobilized (plate-coated) anti-TCR Vβ13.1 antibody (A-H.1) or anti-CD3 antibody (OKT3) at 100 nM for 6 days. Activated T-cells (from plate-coated) were then prepared for gene expression profiling (PanCancer IO 360™ Panel, nanoString), following manufacturer's protocol. Differential gene expression analysis was grouped by anti-TCR Vβ13.1 (A-H.1) vs anti-CD3 (OKT3) activated T-cells using the nSolver Analysis Software (Nanostring). Data shown in Table 15A are mean values from 3 donors. The differentially regulated genes shown in Table 15A have a p-value of 0.05 or less. In the fourth column of Table 15A showing fold changes in gene expression, a positive value indicates genes that are upregulated at the transcriptional level in TCR Vβ-activated T cells compared to OKT3-activated T cells, whereas a negative value indicates genes downregulated at the transcriptional level in TCR Vβ-activated T cells compared to OKT3-activated T cells.

TABLE 15A

Summary of genes whose expression are preferentially regulated in TCR Vβ-activated T cells compared to OKT3-activated T cells.

Probe Name	Accession #	NS Probe ID	TCR Vβ13.1 vs OKT3 Fold Change	P value
CCR2	NM_001123041.2	NM_001123041.2: 743	−3.06	0.00019145
LIF	NM_002309.3	NM_002309.3: 1240	21.6	0.0003319
TCF7	NM_003202.2	NM_003202.2: 2420	−8.38	0.00037035
PLA2G6	NM_001004426.1	NM_001004426.1: 1954	−2.19	0.00043564
CD84	NM_001184879.1	NM_001184879.1: 28	−3.81	0.00062413
ITGB2	NM_000211.2	NM_000211.2: 520	−2.11	0.0012003
GZMK	NM_002104.2	NM_002104.2: 700	−11.09	0.00135083
HLA-DRB4	NM_021983.4	NM_021983.4: 194	−5.75	0.00137591
CCR7	NM_001838.2	NM_001838.2: 1610	−2.43	0.00165716
PDCD1	NM_005018.1	NM_005018.1: 175	7.24	0.00195468
CD96	NM_005816.4	NM_005816.4: 1355	−6.44	0.00221401
SELL	NR_029467.1	NR_029467.1: 1585	−5	0.00227156
NFATC4	NM_001136022.2	NM_001136022.2: 2296	−2.75	0.0025171
CD8B	NM_004931.3	NM_004931.3: 440	−3.56	0.00302475
NLRC5	NM_032206.4	NM_032206.4: 860	−2.27	0.00309164
CD1C	NM_001765.2	NM_001765.2: 750	8.62	0.0035729
HLA-B	NM_005514.6	NM_005514.6: 937	−1.81	0.00363669
NUP107	NM_020401.2	NM_020401.2: 1002	1.64	0.00366886
CD3D	NM_000732.4	NM_000732.4: 110	−2.05	0.00401569
HDAC3	NM_003883.2	NM_003883.2: 1455	−1.41	0.0042794
PRKCE	NM_005400.2	NM_005400.2: 1695	−1.86	0.00429076
HLA-DQB1	NM_002123.3	NM_002123.3: 384	−5.71	0.00430297
AKT3	NM_181690.1	NM_181690.1: 755	−2.98	0.00430433
VCAM1	NM_001078.3	NM_001078.3: 2535	−23.93	0.00464703
CD53	NM_001040033.1	NM_001040033.1: 835	−1.7	0.00507702
LRP1	NM_002332.2	NM_002332.2: 4240	−2.22	0.00508974
CD28	NM_001243078.1	NM_001243078.1: 2065	−1.73	0.00545641
OSM	NM_020530.4	NM_020530.4: 580	8.97	0.00558554
CLEC4A	NM_194448.2	NM_194448.2: 388	−1.7	0.0056661
MFGE8	NM_001114614.1	NM_001114614.1: 328	−2.75	0.00633707
IFNAR2	NM_000874.3	NM_000874.3: 631	−3.69	0.00659279

TABLE 15A-continued

Summary of genes whose expression are preferentially regulated in TCR Vβ-activated T cells compared to OKT3-activated T cells.

Probe Name	Accession #	NS Probe ID	TCR Vβ13.1 vs OKT3 Fold Change	P value
LTA	NM_000595.2	NM_000595.2: 885	6.53	0.00727884
ITGAE	NM_002208.4	NM_002208.4: 3405	−3.42	0.00779862
CXCR5	NM_001716.3	NM_001716.3: 2618	4.38	0.00781195
CD6	NM_006725.3	NM_006725.3: 1280	−1.38	0.00848703
ICOS	NM_012092.2	NM_012092.2: 640	1.74	0.00914866
NOS2A	NM_153292.1	NM_153292.1: 546	−2.29	0.0095337
CD1A	NM_001763.2	NM_001763.2: 1815	5.12	0.00956367
CD27	NM_001242.4	NM_001242.4: 330	−3.41	0.00984676
KLRD1	NM_002262.3	NM_002262.3: 542	−6.43	0.00998325
TARP	NM_001003799.1	NM_001003799.1: 560	−3.71	0.00998698
HLA-DPB1	NM_002121.4	NM_002121.4: 931	−8.85	0.01064161
PTPRC	NM_080921.3	NM_080921.3: 258	−2.86	0.01124117
CD44	NM_001001392.1	NM_001001392.1: 429	−2.07	0.01138242
SLAMF6	NM_001184714.1	NM_001184714.1: 1032	−1.81	0.00175123
HLA-DMB	NM_002118.3	NM_002118.3: 20	−6.39	0.01184625
CD276	NM_001024736.1	NM_001024736.1: 2120	6.22	0.01207813
MAGEA1	NM_004988.4	NM_004988.4: 476	−2.93	0.01210408
HLA-DMA	NM_006120.3	NM_006120.3: 380	−5.75	0.1210789
EP300	NM_001429.2	NM_001429.2: 715	−1.24	0.01228626
ADA	NM_000022.2	NM_000022.2: 1300	−2.97	0.01228787
ICAM1	NM_000201.2	NM_000201.2: 2253	2.52	0.01290081
SIGIRR	NM_021805.2	NM_021805.2: 469	−4.46	0.01309473
TNF	NM_000594.2	NM_000594.2: 1010	4.6	0.01318389
IL1RAP	NM_002182.2	NM_002182.2: 460	2.77	0.01329693
CSF1	NM_000757.4	NM_000757.4: 823	2.55	0.01373637
CD40LG	NM_000074.2	NM_000074.2: 1225	11.92	0.01376174
CYFIP2	NM_001037332.2	NM_001037332.2: 4043	−1.38	0.01389707
MUC1	NM_001018017.1	NM_001018017.1: 725	3.12	0.01399543
HLA-DRB3	NM_022555.3	NM_022555.3: 698	−7.11	0.01404049
CD2	NM_001767.3	NM_001767.3: 687	−1.53	0.01432842
IL2RG	NM_000206.1	NM_000206.1: 595	−1.82	0.01477006
HLA-A	NM_002116.5	NM_002116.5: 1000	−1.96	0.01454336
TXK	NM_003328.1	NM_003328.1: 800	−2.7	0.01590341
ITGA4	NM_000885.4	NM_000885.4: 975	−3.59	0.01601785
DHX16	NM_001164239.1	NM_001164239.1: 2490	1.41	0.0167432
CD3E	NM_000733.2	NM_000733.2: 75	−1.52	0.01736902
MR1	NM_001531.2	NM_001531.2: 7695	−2.26	0.01744764
SMAD3	NM_005902.3	NM_005902.3: 4220	−2.82	0.01751245
CCRL2	NM_003965.4	NM_003965.4: 1110	−1.87	0.01834479
HRAS	NM_005343.2	NM_005343.2: 396	1.97	0.0187379
IL18R1	NM_003855.2	NM_003855.2: 2025	2.36	0.01896204
CMA1	NM_001836.2	NM_001836.2: 561	−1.96	0.01964938
PSMB7	NM_002799.2	NM_002799.2: 420	1.53	0.01980367
BCL10	NM_003921.2	NM_003921.2: 1250	−1.38	0.01981376
HLA-DRA	NM_019111.3	NM_019111.3: 335	−7.46	0.02026993
CD80	NM_005191.3	NM_005191.3: 1288	4.18	0.02055337
PIK3CD	NM_005026.3	NM_005026.3: 2978	−1.23	0.02056576
ETS1	NM_005238.3	NM_005238.3: 4625	−1.51	0.02083359
CHUK	NM_001278.3	NM_001278.3: 860	1.67	0.0217326
CCL5	NM_002985.2	NM_002985.2: 280	−2.47	0.02195802
ITGAL	NM_002209.2	NM_002209.2: 3905	−3	0.02244779
TNFRSF18	NM_004195.2	NM_004195.2: 445	−3.76	0.02330885
EIF2B4	NM_172195.3	NM_172195.3: 1390	1.28	0.02349098
CD79A	NM_001783.3	NM_001783.3: 695	−4.47	0.02361746
ABCF1	NM_001090.2	NM_001090.2: 850	1.31	0.02452054
CD37	NM_001774.2	NM_001774.2: 535	−2.06	0.02476513
STAT5B	NM_012448.3	NM_012448.3: 200	−1.56	0.02495121
CSF2	NM_000758.2	NM_000758.2: 475	11.38	0.0256982
STAT3	NM_139276.2	NM_139276.2: 4535	−1.47	0.02629936
GZMA	NM_006144.2	NM_006144.2: 155	−2.46	0.02646368
C1R	NM_001733.4	NM_001733.4: 760	−3.1	0.02653879
MIF	NM_002415.1	NM_002415.1: 319	−1.38	0.02690018
CD46	NM_172350.1	NM_172350.1: 365	−1.36	0.02725208
PIK3CG	NM_002649.2	NM_002649.2: 2125	−2.34	0.02762105
CFB	NM_001710.5	NM_001710.5: 2029	−2.59	0.02802998
IL3	NM_000588.3	NM_000588.3: 130	13.37	0.02820076
TNFRSF13C	NM_052945.3	NM_052945.3: 789	−2.2	0.02835259
MRPS5	NM_031902.3	NM_031902.3: 390	1.2	0.02849936
TUBB	NM_178014.2	NM_178014.2: 320	1.06	0.02874459
PECAM1	NM_000442.3	NM_000442.3: 1365	−4.35	0.02901845
PVR	NM_006505.3	NM_006505.3: 604	2.28	0.0299334
AMICA1	NM_153206.2	NM_153206.2: 620	−2.38	0.03034954
CD74	NM_001025159.1	NM_001025159.1: 964	−3.28	0.0305419
ENTPD1	NM_001098175.1	NM_001098175.1: 8830	−8.02	0.03085618

TABLE 15A-continued

Summary of genes whose expression are preferentially regulated in TCR Vβ-activated T cells compared to OKT3-activated T cells.

Probe Name	Accession #	NS Probe ID	TCR Vβ13.1 vs OKT3 Fold Change	P value
CD97	NM_078481.2	NM_078481.2: 1370	−1.56	0.03086014
KLRK1	NM_007360.3	NM_007360.3: 522	−4.16	0.03108504
HLA-DQA1	NM_002122.3	NM_002122.3: 261	−5.51	0.03126291
CD247	NM_198053.1	NM_198053.1: 1490	−1.88	0.03182703
IFNG	NM_000619.2	NM_000619.2: 970	5.98	0.03202586
SAA1	NM_199161.1	NM_199161.1: 135	−2.35	0.03341258
TBX21	NM_013351.1	NM_013351.1: 890	1.92	0.03359165
RORA	NM_134261.2	NM_134261.2: 1715	−2.57	0.03591525
MASP2	NM_139208.1	NM_139208.1: 330	−1.65	0.03611762
CLU	NM_001831.2	NM_001831.2: 2340	−1.55	0.0369776
KLRB1	NM_002258.2	NM_002258.2: 85	−7.43	0.03705134
RELA	NM_021975.2	NM_021975.2: 360	−1.26	0.03765981
SLAMF1	NM_003037.2	NM_003037.2: 580	1.82	0.03768168
CD8A	NM_001768.5	NM_001768.5: 1320	−4.49	0.0380276
IL11RA	NM_147162.1	NM_147162.1: 400	−3.54	0.03855863
CD3G	NM_000073.2	NM_000073.2: 404	−1.44	0.03877635
JAK1	NM_002227.1	NM_002227.1: 285	−1.84	0.4001383
SPN	NM_003123.3	NM_003123.3: 2345	−1.72	0.04035383
CXCR4	NM_003467.2	NM_003467.2: 1335	−3.03	0.04122601
FAS	NM_000043.3	NM_000043.3: 90	−2.37	0.04150638
IL2	NM_000586.2	NM_000586.2: 300	10.9	0.04175377
ITGA1	NM_181501.1	NM_181501.1: 1875	−2.75	0.04213304
IGF1R	NM_000875.2	NM_000875.2: 455	−1.94	0.0424234
CLEC6A	NM_001007033.1	NM_001007033.1: 342	−2.83	0.04299769
RPS6	NM_001010.2	NM_001010.2: 171	−1.36	0.04334091
MAPK11	NM_002751.5	NM_002751.5: 1310	−1.98	0.04344288
REL	NM_002908.2	NM_002908.2: 225	−2.37	0.04382344
EOMES	NM_005442.2	NM_005442.2: 1670	−6.49	0.04442535
KLRG1	NM_005810.3	NM_005810.3: 65	−3.52	0.04487411
IL2RA	NM_000417.1	NM_000417.1: 1000	3.4	0.0457568
IFNA17	NM_021268.2	NM_021268.2: 291	−3.13	0.04595868
SH2D1B	NM_053282.4	NM_053282.4: 545	−1.44	0.04640447
CCL2	NM_002982.3	NM_002982.3: 123	4.01	0.04660539
TXNIP	NM_006472.1	NM_006472.1: 255	−4.07	0.04695375
CXCL13	NM_006419.2	NM_006419.2: 210	−65.05	0.04708191
CASP8	NM_001228.4	NM_001228.4: 301	−1.42	0.04720592
MTMR14	NM_022485.3	NM_022485.3: 720	−1.25	0.04798024
MAP3K5	NM_005923.3	NM_005923.3: 1760	−1.62	0.04838454
ADORA2A	NM_000675.3	NM_000675.3: 1095	1.3	0.04872028
CCR5	NM_000579.1	NM_000579.1: 2730	−4.01	0.04885927

In a second study, the multispecific anti-TCR Vβ13.1/anti-BCMA antibody Molecule H was compared with the anti-CD3 antibody OKT3. Purified T cells were stimulated with solid-phase anti-TCR Vβ antibody over 6 days with the anti-TCR Vβ antibody Molecule H or anti-CD3e antibody (OKT3) at 100 nM. Expanded T cells were collected by centrifugation followed by RNA extraction. Seven hundred and seventy eight (778) immunology-related genes were counted using the nCounter Technology (Nanostring) followed by gene expression analysis using nSolver analysis tools. The data described in this Example is representative of 3 donors.

Based on this analysis, a panel of genes were identified as being differentially regulated in TCR Vβ-activated T cells compared to OKT3-activated T cells (Table 15B). The differentially regulated genes shown in Table 15B have a p-value of 0.05 or less. For example, LIF, CD40LG, PDCD1, CXCR5, LTA, and CD80 are all upregulated at the transcriptional level in TCR Vβ-activated T cells compared to OKT3-activated T cells. GZMK, ENTPD1 (CD39), TCF7, CD96, HLA-DRB4, SIGIRR and SELL are downregulated at the transcriptional level in TCR Vβ-activated T cells compared to OKT3-activated T cells. TCR Vβ-activated T cells also expressed high levels of cytolytic effectors (e.g., IFNg, Granzyme B and perforin).

TABLE 15B

Summary of genes whose expression are preferentially regulated in TCR Vβ-activated T cells compared to OKT3-activated T cells.

Gene	Description	Log_2 Fold Change	P-Value
LIF	LIF Interleukin 6 Family Cytokine	4.65	0.0119
GZMK	Granzyme K	−3.65	0.0468
CD40LG	CD40 Ligand	3.56	0.0082
ENTPD1 (CD39)	Ectonucleoside Triphosphate Diphosphohydrolase 1	−3.53	0.0541
PDCD1	Programmed Cell Death 1	3.19	0.0257
TCF7	Transcription Factor 7	−3.1	0.00634
CXCR5	Chemokine receptor for CXCL13	3.05	0.0337
CD96	Transmembrane glycoprotein Ig superfamily receptor, interacts with nectin and nectin-like proteins, including CD155/polio virus receptor (PVR)	−2.75	0.007
LTA	Lymphotoxin Alpha	2.67	0.0082
HLA-DRB4	Major Histocompatibility Complex, Class II, DR Beta 4	−2.66	0.0377
CD80	T cell costimulatory molecule	2.58	0.0425
SIGIRR	Single Ig And TIR Domain Containing	−2.37	0.0227
SELL	Selection L	−2.3	0.00634

Example 12: Binding Affinity of Affinity Matured Humanized Antibody A-H Antibodies

This Example describes the evaluation of binding affinity of affinity matured humanized Antibody A-H antibodies to recombinant protein TCRVB 6-5.

Antibody A-H humanized antibodies were affinity matured. The resulting affinity matured antibodies were tested for their binding affinity to TCRVB 6-5 as described below.

TCRVB 6-5 at 5 ug/mL was immobilized on a Biotin CAP Series S Sensor Chip to 60 RU. BJM0277 was diluted to 200 nM and then serially diluted two fold. Association was 120 seconds, and dissociation was 300 seconds. This assay was run in 1×HBS-EP+ Buffer pH 7.4 and 25 C. The data was fit using a 1:1 binding model.

TCRVB 6-5 at 5 ug/mL was immobilized on a Biotin CAP Series S Sensor Chip to 60 RU. A-H.45 was diluted to 50 nM and then serially diluted two fold. Association was 120 seconds, and dissociation was 300 seconds. This assay was run in 1×HBS-EP+ Buffer pH 7.4 and 25 C. The data was fit using a 1:1 binding model. A-H.45 is an improved yeast clone (TCRvB/CD19 bispecific) and contains a mutation (G to V) at the last residue in framework 3, just before HCDR3. The affinity is 35-fold greater than the BJM0277 (Table 16).

TCRVB 6-5 at 5 ug/mL was immobilized on a Biotin CAP Series S Sensor Chip to 60 RU. A-H.52 was diluted to 50 nM and then serially diluted two fold. Association was 120 seconds, dissociation was 300 seconds. This assay was run in 1×HBS-EP+ Buffer pH 7.4 and 25 C. The data was fit using a 1:1 binding model. A-H.52 is a phage clones and is a monovalent scFv. A-H.52 has two mutations on CDRH1. The affinity of A-H.52 is 20-fold greater than BJM0277 (Table 16).

TCRVB 6-5 at 5 ug/mL was immobilized on a Biotin CAP Series S Sensor Chip to 60 RU. A-H.53 was diluted to 50 nM and then serially diluted two fold. Association was 120 seconds, dissociation was 300 seconds. This assay was run in 1×HBS-EP+ Buffer pH 7.4 and 25 C. The data was fit using a 1:1 binding model. A-H.53 (phage clone) affinity is in the pM range (Table 16). The affinity of A-H.53 is 200-fold greater than BJM0277 (Table 16).

TCRVB 6-5 at 5 ug/mL was immobilized on a Biotin CAP Series S Sensor Chip to 60 RU. A-H.54 was diluted to 50 nM and then serially diluted two fold. Association was 120 seconds, dissociation was 300 seconds. This assay was run in 1×HBS-EP+ Buffer pH 7.4 and 25 C. The data was fit using a 1:1 binding model. A-H.54 (phage clone) affinity is 17-fold greater than BJM0277 (Table 16).

TABLE 16

Summary of affinity maturation of anti-TCRVb antibodies

Construct	Target: TCRVβ 6-5
BJM0277	35 nM
A-H.45	1.08 Nm
A-H.52	1.76 nM
A-H.53	165 pM
A-H.54	2.22 nM

Example 13: Therapeutic Efficacy of CD19/TCRvB Bispecific Molecules in Subcutaneous Human Tumor Xenograft Models

This Example demonstrates the in vivo efficacy of a CD19/TCRvB Bispecific molecule in a subcutaneous human tumor animal model.

On day 1 of the study 1×10^6 cells of the human cancer cell line Raji, stably expressing firefly luciferase (Raji-luc) were subcutaneously injected in the right dorsal flank of female NOD/SCID/IL-2Rγnull (NSG) mice. On day 3, 10×10^6 human PBMCs were transplanted into mice by injection into the peritoneal cavity.

Antibody treatment started at day 10, when tumors had reached a mean tumor volume (TV) of 80 mm^3. Mean TV of each group was not statistically different from any other group at start of treatment. Mice were treated with 0.2 mg/kg, 1 mg/kg and 5 mg/kg of CD19/TCRvB bispecific molecule every three days for a total of 7 doses by intravenous bolus injection.

Tumor volume (TV) was measured every 3 days by calipers and progress evaluated by intergroup comparison of TV. Tumor growth inhibition T/C [%] was calculated as T/C[%]=100×(mean TV of analyzed group)/(mean TV of vehicle group).

Results are shown in Table 17 and FIG. **28**. Treatment with the CD19/TCRvB Bispecific molecule inhibited tumor growth compared to vehicle control treatment (FIG. **28**). The results demonstrate that the CD19/TCRvB bispecific molecule inhibits tumor growth and has anti-tumor activity.

TABLE 17

Mean tumor volume and tumor growth inhibition (T/C) at days 10 to 28.

Dose group	Data	D10	D13	D16	D19	D23	D25	D28
Vehicle	TV (mm^3)	84	241	566	802	1577	2161	2478
	T/C [%]	100	100	100	100	100	100	100
0.2 mg/kg CD19/TCRvB	TV (mm^3)	82	169	460	643	967	946	875
	T/C [%]	98	70	81	80	61	44	35
1 mg/kg CD19/TCRvB	TV (mm^3)	82	122	147	307	482	469	406
	T/C [%]	98	51	26	38	31	22	16
5 mg/kg CD19/TCRvB	TV (mm^3)	79	160	200	381	510	409	382
		94	66	35	48	32	19	15

Example 14: Therapeutic Efficacy of CD19/TCRvB Bispecific Molecules in Human Tumor Xenograft Models

This Example demonstrates the in vivo efficacy of a CD19/TCRvB Bispecific molecules in a xenograft animal model.

On day 1 of the study 10×10^6 human PBMCs were transplanted into NOD/SCID/IL-2Rγnull (NSG) mice by injection into the peritoneal cavity.

On day 7, 1×10^6 cells of the human cancer cell line Raji, stably expressing firefly luciferase (Raji-luc) were intravenously injected into NOD/SCID/IL-2Rγnull (NSG) mice. Control animals were injected with 10×10^6 cells of the CD19 negative human cancer cell line K562 stably expressing firefly luciferase (K562-luc). These animals were used to assess specific killing ability of CD19/TCRvB molecules. Antibody treatment started at day 16, when tumor engraftment had reached a mean bioluminescence flux level of 4×10^7 photons/s. Mean Flux level of each group was not statistically different from any other group at start of treatment. Mice were treated with 1 mg/kg and 5 mg/kg of CD19/TCRvB bispecific molecule every three days for a total of 6 doses by intravenous bolus injection.

Tumor burden was measured weekly by bioluminescence imaging and progress evaluated by intergroup comparison of total bioluminescence flux (Total Flux). Tumor growth inhibition T/C [%] was calculated as T/C[%]=100×(mean Total Flux of analyzed group)/(mean Total Flux of vehicle group).

The results for Raji-luc engrafted animals are shown in Table 18 and FIG. **29**A and results for K562-luc engrafted animals are shown in Table 19 and FIG. **29**B. The results demonstrate that the CD19/TCRvB bispecific molecule inhibits tumor growth and has anti-tumor activity (FIG. **29**A and Table 18).

TABLE 18

Mean tumor burden (Total Flux) and tumor growth inhibition (T/C) at days 16 to 37 in animals engrafted with Raji-luc cells

Dose group	Data	D 16	D 23	D 30	D 37
Vehicle	Total Flux (p/s)	4.26E+07	5.92E+07	5.77E+08	4.23E+09
	T/C[%]	100	100	100	100
1 mg/kg CD19/TCRvB	Total Flux (p/s)	4.05E+07	2.66E+07	5.03E+07	5.42E+08
	T/C[%]	95.0	44.9	8.7	12.8
5 mg/kg CD19/TCRvB	Total Flux (p/s)	4.18E+07	3.10E+07	2.37E+07	1.44E+08
	T/C[%]	98.0	52.3	4.1	3.4

TABLE 19

Mean tumor burden (Total Flux) and tumor growth inhibition (T/C) at days 16 to 30 in animals engrafted with K562-luc cells

Dose group	Data	D 16	D 23	D 30
Vehicle	Total Flux (p/s)	2.98E+07	9.94E+08	2.40E+10
	T/C[%]	100	100	100
5 mg/kg CD19/TCRvB	Total Flux (p/s)	2.00E+07	1.22E+09	3.82E+10
	T/C[%]	67.0	122.4	159.4

Example 15: Therapeutic Efficacy of BCMA/TCRvB Bispecific Molecules in Human Tumor Xenograft Models

This Example demonstrates the in vivo efficacy of a BCMA/TCRvB Bispecific molecule in a xenograft animal model.

On day 1, 20×10^6 cells of the human cancer cell line RPMI-8226, stably expressing firefly luciferase (RPMI-8226-luc) were intravenously injected into NOD/SCID/IL-2Rγnull (NSG) mice. On day 11, 10×10^6 human PBMCs were transplanted into mice by injection into the peritoneal cavity. Antibody treatment started at day 17, when tumor engraftment had reached a mean bioluminescence flux level of 4×10^7 photons/s. Mice were treated with 0.5 mg/kg of a molecule bivalent for both BCMA and TCRvB (2×2 molecule) and 0.5 mg/kg of a molecule bivalent for BCMA and monovalent for TCRvB (2×1 molecule) once a week for a total of 2 doses by intravenous bolus injection.

Tumor burden was measured weekly by bioluminescence imaging and progress evaluated by intergroup comparison of total bioluminescence flux (Total Flux). Tumor growth inhibition T/C [%] was calculated as T/C[%]=100×(mean Total Flux of analyzed group)/(mean Total Flux of vehicle group).

Results of these studies are shown in Table 20 and FIG. **30**. Treatment with the BCMA/TCRvB Bispecific molecule inhibited tumor growth compared to vehicle control treatment (FIG. **29**). The results demonstrate that the BCMA/TCRvB bispecific molecule inhibits tumor growth and has anti-tumor activity.

TABLE 20

Mean tumor burden (Total Flux) and tumor growth inhibition (T/C) at days 16 to 30.

Dose group	Data	D 16	D 23	D 30
Vehicle	Total Flux (p/s)	3.71E+06	6.04E+06	7.29E+06
	T/C[%]	100	100	100
0.5 mg/kg BCMA/TCRvB 2 × 2	Total Flux (p/s)	7.33E+06	6.30E+06	1.13E+06
	T/C[%]	197.7	104.3	15.5
0.5mg/kg BCMA/TCRvB 2 × 1	Total Flux (p/s)	3.66E+06	3.15E+06	5.65E+05
	T/C[%]	98.8	52.1	7.8

Example 16: Expression and Purification of Antibody Constructs

Construction of the Plasmids

The DNA encoding the protein sequences was optimized for expression in *Cricetulus griseus*, synthesized, and cloned into the pcDNA3.4-TOPO (Life Technologies A14697) using Gateway cloning. All constructs contained an Ig Kappa leader sequence METDTLLLWVLLLWVPGSTG (SEQ ID NO: 3288).

Expression and Purification

The plasmids were co-transfected into either Expi293 cells (Life Technologies A14527) or ExpiCHO cells (Life Technologies A29127). Transfections were performed using 1 mg of total DNA for a multi specific construct with a 1:1 heavy chain ratio and 3:2 light chain to heavy chain ratio if applicable. Transfection in Expi293 cells was done using linear 25,000 Da polyethylenimine (PEI, Polysciences Inc 23966) in a 3:1 ratio with the total DNA. The DNA and PEI were each added to 50 mL of OptiMem (Life Technologies 31985088) medium and sterile filtered. The DNA and PEI were combined for 10 minutes and added to the Expi293 cells with a cell density of 1.8-2.8×10^6 cells/mL and a viability of at least 95%. The ExpiCHO transfection was performed according to the manufacturer's instructions. Expi293 cells were grown in a humidified incubator at 37° C. with 8% CO_2 for 5-7 days after transfection and ExpiCHO cells were grown for 14 days at 32° C. with 5% CO_2. The cells were pelleted by centrifugation at 4500×g and the supernatant was filtered through a 0.2 μm membrane. Protein A resin (GE 17-1279-03) was added to the filtered supernatant and incubated for 1-3 hours at room temperature. The resin was packed into a column, washed with 3×10 column volumes of Dulbecco's phosphate-buffered saline (DPBS, Life Technologies 14190-144). The bound protein was eluted from the column with 20 mM citrate, 100 mM NaCl, pH 2.9. When necessary, the proteins were further purified using ligand affinity and/or size exclusion chromatography on a Superdex 200 column with a running buffer of DPBS.

Example 17: Humanization of Anti-TRBV5-5 Antibody Clone Antibody C

The germline for the mouse anti-TCRvbeta antibody clone Antibody C VH and VL were assigned using IMGT nomenclature, with CDR regions defined by a combined Kabat and Chothia classification. SEQ ID NO: 232 and SEQ ID NO: 233 are the Antibody C VH and VL sequences respectively where the VH germline is mouse IGHV2-6-7*01 and the VL germline is mouse IGKV10-94*02. The method applied to humanize Antibody A described in Example 1 was used to humanize Antibody C. The Antibody C VH was humanized into human IGHV2-26*01, IGHV2-70*04, IGHV4-4*02, IGHV2-5*09, IGHV2-5*08, IGHV4-34*09, IGHV4-59*01, IGHV4-59*07, IGHV4-61*02, IGHV4-38-2*01, IGHV4-31*01, IGHV3-49*04, IGHV3-49*02, IGHV4-4*07, IGHV3-49*05, IGHV4-34*10, IGHV4-28*04, IGHV3-72*01, IGHV3-15*07, IGHV6-1*01, IGHV3-7*01, IGHV4-34*01, IGHV3-33*02, IGHV3-48*02, IGHV3-23*03, IGHV3-21*01, IGHV3-73*01, IGHV3-30*02, IGHV3-7*01, IGHV3-43*01, and IGHV3-53*03 and the Antibody C VL was humanized into human IGKV1D-43*01, IGKV1-27*01, IGKV1-17*02, IGKV1-17*01, IGKV1-5*01, IGKV4-1*01, IGKV3-7*02, IGKV3-7*01, IGKV2-29*02, IGKV6D-41*01, IGKV2-28*01, IGKV2-40*01, IGKV3-15*01, IGKV2-24*01, IGKV6-21*01, IGKV2D-26*01, and IGKV2D-26*03.

SEQ ID NOs: 3040-3089 are the Antibody C humanized heavy chains and SEQ ID NOs: 3000-3039 are the Antibody C humanized light chains (as described in Table 10).

Example 18: Humanization of TRBV10-1, TRBV10-2, and TRBV10-3 Antibody Clone Antibody D

The germline for the mouse anti-TCRvbeta antibody clone Antibody D VH and VL were assigned using IMGT nomenclature, with CDR regions defined by a combined Kabat and Chothia classification. SEQ ID NO: 3183 and SEQ ID NO: 3184 are the Antibody D VH and VL sequences respectively where the VH germline is mouse IGHV5-6*01 and the VL germline is mouse IGKV4-59*01.

The method applied to humanize Antibody A described in Example 1 was used to humanize Antibody D. The Antibody D VH was humanized into human IGHV3-30*03, IGHV3-30*02, IGHV3-7*01, IGHV3-21*01, IGHV3-23*04, IGHV3-30*15, IGHV3-48*02, IGHV3-53*04, IGHV3-23*03, IGHV3-53*03, IGHV3-53*01, IGHV3-9*01, IGHV3-30*13, IGHV3-20*01, IGHV3-43D*03, IGHV3-43*02, IGHV3-43*01, IGHV3-53*02, IGHV3-13*01, IGHV3-38-3*01, IGHV3-9*03, IGHV3-64D*06, IGHV3-33*02, IGHV3-11*03, IGHV3-64*02, IGHV3-64*01, IGHV3-64*03, IGHV3-7*01, IGHV3-35*01, IGHV3-13*02, IGHV3-38*02, and IGHV3-38*01 and the Antibody D VL was humanized into human IGKV3-11*01, IGKV1-13*02, IGKV1-9*01, IGKV6-21*01, IGKV1D-43*01, IGKV3-11*01, IGKV3D-11*02, IGKV1-17*03, IGKV3D-20*01, IGKV3-20*01, IGKV1D-16*01, IGKV4-1*01, IGKV2-28*01, IGKV2-40*01, IGKV2-29*02, IGKV2-29*01, IGKV1D-42*01, IGKV2-24*01, and IGKV5-2*01. SEQ ID NOs: 3225-3274 are the Antibody D humanized heavy chains and SEQ ID NOs: 3185-3224 are the Antibody D humanized light chains (as described in Table 12).

Example 19: Humanization of TRBV5-5 and TRBV5-6 Antibody Clone Antibody E

The germline for the mouse anti-TCRβ antibody clone Antibody E VH and VL were assigned using IMGT nomenclature, with CDR regions defined by a combined Kabat and Chothia classification. SEQ ID NO: 3091 and SEQ ID NO: 3092 are the Antibody E VH and VL sequences respectively where the VH germline is mouse IGHV1-82*01 and the VL germline is mouse IGKV3-5*01.

The method applied to humanize Antibody A described in Example 1 was used to humanize Antibody E. The Antibody E VH was humanized into human IGHV1-69*08, IGHV1-3*02, IGHV1-18*03, IGHV1-3*01, IGHV1-18*01, IGHV1-2*06, IGHV1-2*01, IGHV1-2*06, IGHV1-8*01, IGHV7-4-1*02, IGHV1-58*02, IGHV5-51*01, IGHV7-4-1*04, IGHV7-81*01, IGHV5-51*04, IGHV5-51*01, IGHV1-45*03, IGHV3-49*04, IGHV3-49*02, IGHV3-49*05, IGHV4-4*02, IGHV3-49*05, IGHV3-73*01, IGHV4-4*02, IGHV3-15*07, IGHV3-15*02, IGHV3-72*01, IGHV4-59*07, IGHV4-31*01, IGHV4-31*02, IGHV3-30*15, IGHV3-21*01, IGHV3-7*01, IGHV4-28*01, IGHV4-28*02, IGHV3-30*08, IGHV3-30*05, and IGHV3-30*01 and the Antibody E VL was humanized into human IGKV4-1*01, IGKV3-11*01, IGKV3-20*02, IGKV3-11*01, IGKV1-13*02, IGKV3D-11*01, IGKV3D-20*02, IGKV1-13*02, IGKV3D-20*01, IGKV1-9*01, IGKV3D-15*03, IGKV3-15*01, IGKV1-5*01, IGKV2D-

29*01, IGKV3-7*02, IGKV1-9*01, IGKV2-28*01, IGKV2-40*01, IGKV2D-29*02, IGKV3-7*01, IGKV2-30*01, IGKV2-24*01, IGKV6D-41*01, IGKV1D-42*01, IGKV2D-26*01, IGKV2D-26*03, and IGKV5-2*01. SEQ ID NOs: 3133-3182 are the Antibody E humanized heavy chains and SEQ ID NOs: 3093-3132 are the Antibody E humanized light chains (as described in Table 11).

Example 20: In Vitro Cytotoxicity of an Anti-TCRVb/CD19 Antibody Molecule and an Anti-TCRVb/BCMA Antibody Molecule

Anti-TCR/Anti-CD19 Dual Targeting Antibody Molecule

Human PBMCs were isolated from whole blood. From isolated PBMCs, human CD3+ T cells were isolated using magnetic-bead separation (negative selection) (Miltenyi biotec) and activated by immobilized (plate-coated) anti-TCR Vβ13.1 (A-H.1) at 100 nM for 6 days. Activated T-cells (from plate-coated) were then transferred and expanded in tissue culture flask in the presence of human IL-2 at a concentration of 50 U/ml for two additional days. Expanded TCR Vβ13.1+ cells were washed and co-cultured in the presence of CD19-expressing Raji cells (target cells) at an E:T ratio of 5:1 and serial diluted concentrations of T-cell engager bispecific antibodies including, anti-TCR Vβ13.1/CD19 (Molecule F), anti-CD3/CD19, and anti-TCR Vβ13.1 (A-H.1, serving as control) for 24 hours. Post 24 hours, cell co-culture supernatants were collected and quantified for specific target cell death. Target cells (Raji cells) are a KILR-retroparticles reporter cell assay (DiscoverX). KILR-Raji target cells are engineered to stably express a protein tagged with enhanced. ProLabel (ePL), a β-gal reporter fragment, using the KILR Retroparticles, and when the membrane of the target cells is compromised due to cell death, the target cells will release the tagged protein into the media. This KILR reporter protein can be detected in the media/supernatant by the addition of detection reagents containing the enzyme acceptor (EA) fragment of the β-gal reporter. This leads to the formation of the active gal enzyme which hydrolyzes the substrate to give a chemiluminescent output (RLU). Percentage (%) of target cell death is calculated using the following formula:

(RLU Treatment−RLU No Treatment)/(RLU Maximum Lysis RLU No Treatment)×100

Data shown in FIG. **31**A are mean values from 4 donors.

Anti-TCR/Anti-BCMA Dual Targeting Antibody Molecule

Human PBMCs were isolated from whole blood. From isolated PBMCs, human CD3+ T cells were isolated using magnetic-bead separation (negative selection) (Miltenyi biotec) and activated by immobilized (plate-coated) anti-TCR Vβ13.1 (A-H.1) at 100 nM for 6 days. Activated T-cells (from plate-coated) were then transferred and expanded in tissue culture flask in the presence of human IL-2 at a concentration of 50 U/ml for two additional days. Expanded TCR Vβ13.1+ cells were washed and co-cultured in the presence of BCMA-expressing RPMI8226 cells (target cells) at an E:T ratio of 5:1 and serial diluted concentrations of T-cell engager bispecific antibodies including, anti-TCR Vβ13.1/BCMA (Molecule G), anti-CD3/BCMA, and anti-TCR Vβ13.1 (A-H.1, serving as control) for 24 hours. Post 24 hours, cell co-culture supernatants were collected and quantified for specific target cell death. Target cells (RPMI8226 cells) are a KILR-retroparticles reporter cell assay (DiscoverX). KILR-RPMI8226 target cells are engineered to stably express a protein tagged with enhanced ProLabel (ePL), a β-gal reporter fragment, using the MLR Retroparticles, and when the membrane of the target cells is compromised due to cell death, the target cells will release the tagged protein into the media. This Knit reporter protein was detected and percentage (%) of target cell death was calculated as described above. Data shown in FIG. **31**B are mean values from 4 donors.

Example 21: Cytokine Profile of an Anti-TCRVb/BCMA Antibody Molecule

This Examples describes cytokines secreted by PBMCs following activation by the anti-TCR Vβ/anti-BCMA antibody Molecule H. For comparison, activation by an anti-TCR beta constant 1 (TRBC1) antibody Antibody F was also analyzed.

Briefly, human PBMCs were isolated from whole blood followed by solid-phase (plate-coated) stimulation with Molecule H or Antibody F at 100 nM. Supernatant was collected on Days 1, 2, 3, and 5 (for Molecule H) or Days 2 and 5 (for Antibody F) followed by multiplex cytokine analysis for IFNγ, IL-2, IL-1β, IL-6, IL-10, and TNFα, quantified using MSD (Meso Scale Discovery) platform, following the manufacturer's protocol.

As shown in FIGS. **32**A-**32**F and **33**A-**33**F, the cytokine profile of the anti-TCR Vβ/anti-BCMA antibody Molecule H is different from that of the anti-CD3 antibody OKT3 or the anti-TRBC1 Antibody F.

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

Exemplary Embodiments

Disclosed herein are, inter alia, antibody molecules directed to the variable chain of the beta subunit of TCR (TCRβV) which bind and, e.g., activate or expand, T cells, e.g., a subset of T cells ("anti-TCRβV) antibody molecules"). In some embodiments, the anti-TCRβV antibody molecules disclosed herein result in a cytokine profile, e.g., a cytokine secretion profile, that differs from that of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager"). In some embodiments, the anti-TCRβV antibody molecules disclosed herein result in lesser, minimal, or no production of cytokines associated with cytokine release syndrome (CRS), e.g., IL-6, IL-1beta, IL-10 and TNF alpha; and enhanced and/or delayed production of IL-2 and IFN-gamma. In some embodiments, the anti-TCRβV antibodies disclosed herein result in expansion of an immune cell, e.g., a T cell, a tumor infiltrating lymphocyte (TIL), an NK cell, or other immune cells (e.g., as described herein). Also provided herein are methods of making said anti-TCRβV antibody molecules, and methods of using said anti-TCRβV antibody molecules including, methods of using an anti-TCRβV antibody molecule for expanding an immune cell or

an immune cell population, and method of using an anti-TCRβV antibody molecule for treating cancer, including the use as combination therapy with TIL and immune checkpoint therapeutics. This disclosure further provides multispecific molecules, e.g., bispecific molecules, comprising said anti-TCRβV antibody molecules. In some embodiments, compositions comprising anti-TCRβV antibody molecules of the present disclosure, can be used, e.g., to activate and/or redirect T cells to promote tumor cell lysis for cancer immunotherapy. In some embodiments, compositions comprising anti-TCRβV antibody molecules as disclosed herein limit the unwanted side-effects of CRS and/or NT, e.g., CRS and/or NT associated with anti-CD3e targeting.

In some embodiments, the anti-TCRβV antibody molecules disclosed herein result in lesser, minimal, or no production of cytokines associated with cytokine release syndrome (CRS), e.g., IL-6, IL-1beta, IL-10 and TNF alpha; and enhanced and/or delayed production of IL-2 and IFN-gamma, compared with an anti-CD3 antibody molecule (e.g., a low affinity anti-CD3 antibody molecule). In some embodiments, administration of the anti-TCRβV antibody molecules disclosed herein in a subject results in reduced cytokine release syndrome (CRS) (e.g., lesser duration of CRS or no CRS), a reduced severity of CRS (e.g., absence of severe CRS, e.g., CRS grade 4 or 5), reduced neurotoxicity (NT), or a reduced severity of NT, compared with similar administration of an anti-CD3 antibody molecule (e.g., a low affinity anti-CD3 antibody molecule).

Accordingly, provided herein are, anti-TCRβV antibody molecules, multispecific or multifunctional molecules (e.g., multispecific or multifunctional antibody molecules) (also referred to herein as a "composition") that comprise anti-TCRβV antibody molecules, nucleic acids encoding the same, methods of producing the aforesaid molecules, pharmaceutical compositions comprising aforesaid molecules, and methods of treating a disease or disorder, e.g., cancer, using the aforesaid molecules. The antibody molecules and pharmaceutical compositions disclosed herein can be used (alone or in combination with other agents or therapeutic modalities) to treat, prevent and/or diagnose disorders and conditions, e.g., cancer, e.g., as described herein.

In one aspect, the disclosure provides an antibody molecule, e.g., a non-murine, e.g., a human-like (e.g., a human, or humanized antibody molecule), which binds, e.g., specifically binds, to a T cell receptor beta variable (TCRβV) region.

In some embodiments, the anti-TCRBV antibody molecule comprises an antigen binding domain of an antibody disclosed in any of Tables 1-2, or 10-12, or a sequence with at least 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity thereto. In some embodiments, the anti-TCRBV antibody molecule comprises a leader sequence comprising the amino acid sequence of SEQ ID NO: 3288. In some embodiments, the anti-TCRBV antibody molecule does not comprise a leader sequence comprising the amino acid sequence of SEQ ID NO: 3288.

In some embodiments, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a cytokine profile, e.g., a cytokine secretion profile, (e.g., comprising one or more cytokines and/or one or more chemokines), that differs from that of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager").

In some embodiments, the cytokine profile, e.g., cytokine secretion profile, comprises one, two, three, four, five, six, seven, or all of the following:

(i) increased level, e.g., expression level, and/or activity of IL-2;
(ii) reduced level, e.g., expression level, and/or activity of IL-1β;
(iii) reduced level, e.g., expression level, and/or activity of IL-6;
(iv) reduced level, e.g., expression level, and/or activity of TNFα;
(v) reduced level, e.g., expression level, and/or activity of IL-10;
(vi) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours delay, in increased level, e.g., expression level, and/or activity of IL-2;
(vii) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours delay, in increased level, e.g., expression level, and/or activity of IFN-gamma; or
(viii) increased level, e.g., expression level, and/or activity of IL-15, e.g., wherein (i)-(viii) are relative to the cytokine profile, e.g., cytokine secretion profile, of the non-TCRβV-binding T cell engager.

In some embodiments, binding of the anti-TCRBV antibody to a TCRβV region results in reduced cytokine storm, e.g., reduced cytokine release syndrome (CRS) and/or neurotoxicity (NT), as measured by an assay of Example 3, e.g., relative to the cytokine storm induced by the non-TCRβV-binding T cell engager.

In some embodiments, binding of the anti-TCRBV antibody to a TCRβV region results in one, two, three or all of:

(ix) reduced T cell proliferation kinetics;
(x) cell killing, e.g., target cell killing, e.g. cancer cell killing, e.g., as measured by an assay of Example 4;
(xi) increased Natural Killer (NK) cell proliferation, e.g., expansion; or
(xii) expansion, e.g., at least about 1.1-10 fold expansion (e.g., at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold expansion), of a population of memory T cells, e.g., wherein (ix)-(xii) are relative to the non-TCRBV-binding T cell engager.

In some embodiments, an anti-TCRβV antibody molecule disclosed herein recognizes (e.g., binds to), a structurally conserved domain on the TCRβV protein (e.g., as denoted by the circled area in FIG. **24**A).

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, an interface of a TCRβV:TCRalpha complex.

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, a constant region of a TCRβV protein. An exemplary antibody that binds to a constant region of a TCRBV region is JOVI. 1 as described in Viney et al., (*Hybridoma.* 1992 December; 11(6):701-13).

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, one or more (e.g., all) of a complementarity determining region (e.g., CDR1, CDR2 and/or CDR3) of a TCRβV protein.

In some embodiments, binding of the anti-TCRβV antibody molecule to a TCRβV region results in one, two, three, four, five, six, seven, eight, nine, ten or more (e.g., all) of the following:

(i) reduced level, e.g., expression level, and/or activity of IL-1β;
(ii) reduced level, e.g., expression level, and/or activity of IL-6;
(iii) reduced level, e.g., expression level, and/or activity of TNFα;
(iv) increased level, e.g., expression level, and/or activity of IL-2;

(v) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours delay, in increased level, e.g., expression level, and/or activity of IL-2;

(vi) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours delay, in increased level, e.g., expression level, and/or activity of IFN-gamma;

(vii) reduced T cell proliferation kinetics;

(viii) reduced cytokine storm, e.g., cytokine release syndrome (CRS) and/or neurotoxicity (NT), e.g., as measured by an assay of Example 3;

(ix) cell killing, e.g., target cell killing, e.g. cancer cell killing, e.g., as measured by an assay of Example 4;

(x) increased level, e.g., expression level, and/or activity of IL-15; or

(xi) increased Natural Killer (NK) cell proliferation, e.g., expansion.

In some embodiments, any one or all of (i)-(xi) or any combination thereof resulting from an anti-TCRβV antibody molecule disclosed herein is compared to an antibody that binds to: a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments, binding of the anti-TCRβV antibody molecule to a TCRβV region results in secretion, e.g., production of perforin and/or Granzyme B.

In an aspect, the disclosure provides an antibody molecule which binds, e.g., specifically binds, to a T cell receptor beta variable chain (TCRβV) region, wherein the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(a) a light chain variable region (VL) comprising:

(i) one, two or all of (e.g., three) a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 10 or SEQ ID NO: 11; and

(ii) a framework region (FR) having at least 95% identity with one, two, three, or all of (e.g., four) a non-murine germline framework 1 (FR1), a non-murine germline framework region 2 (FR2), a non-murine germline framework region 3 (FR3), and a non-murine germline framework region 4 (FR4); and/or

(b) a heavy chain variable region (VH) comprising:

(i) one, two or all of (e.g., three) a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2) and a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 9; and

(ii) a framework region (FR) having at least 95% identity with one, two, three, or all of (e.g., four) a non-murine germline framework 1 (FR1), a non-murine germline framework region 2 (FR2), a non-murine germline framework region 3 (FR3), and a non-murine germline framework region 4 (FR4).

In some embodiments, the VL comprises a sequence having a consensus sequence of SEQ ID NO: 230 or 3289.

In some embodiments, the VH comprises a sequence having a consensus sequence of SEQ ID NO: 231 or 3290.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV6, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01, or a variant thereof.

In some embodiment, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a HC CDR1, a HC CDR2 and a HC CDR3 of SEQ ID NO: 1 or SEQ ID NO: 9, or an amino acid sequence listed in Table 1; or

(ii) a LC CDR1, a LC CDR2, and a LC CDR3 of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11, or an amino acid sequence listed in Table 1.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a light chain variable region (VL) comprising one, two or all (e.g., three) of a LC CDR1, a LC CDR2 and a LC CDR3 of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11, or an amino acid sequence listed in Table 1.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a heavy chain variable region (VH) comprising one, two or all (e.g., three) of a HC CDR1, a HC CDR2 and a HC CDR3 of SEQ ID NO:1 or SEQ ID NO: 9, or an amino acid sequence listed in Table 1.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a VL comprising: a LC CDR1 amino acid sequence of SEQ ID NO: 6 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a LC CDR2 amino acid sequence of SEQ ID NO:7 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a LC CDR3 amino acid sequence of SEQ ID NO:8 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof); and/or

(ii) a VH comprising: a HC CDR1 amino acid sequence of SEQ ID NO: 3 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a HC CDR2 amino acid sequence of SEQ ID NO:4 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a HC CDR3 amino acid sequence of SEQ ID NO:5 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof).

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

a variable heavy chain (VH) of an amino acid sequence listed in Table 1, e.g., SEQ ID NO: 9, or a sequence having at least about 85%, 90%, 95%, or 99% sequence identity to an amino acid sequence listed in Table 1, e.g., SEQ ID NO: 9; and/or

a variable light chain (VL) of an amino acid sequence listed in Table 1, e.g., SEQ ID NO: 10 or SEQ ID NO: 11, or a sequence having at least about 85%, 90%, 95%, or 99% sequence identity to an amino acid sequence listed in Table 1, e.g., SEQ ID NO: 10 or SEQ ID NO: 11.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) the VH amino acid sequence of SEQ ID NO: 9;

(ii) an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 9;

(iii) the VL amino acid sequence of SEQ ID NO: 10; and/or

(iv) an amino acid sequence having at least about 85%, 90%, 95%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 10.

In an aspect, provided herein is an antibody molecule which binds, e.g., specifically binds, to a T cell receptor beta variable chain (TCRβV) region, wherein the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(a) a light chain variable region (VL) comprising:

(i) one, two or all of (e.g., three) a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3) of a humanized B-H light chain (LC) of Table 2; and

(ii) a framework region (FR) having at least 95% identity with one, two, three or all (e.g., four) of a framework region 1 (FR1), a framework region 2 (FR2), a framework region 3 (FR3), and a framework region 4 (FR4) of a humanized B-H LC of Table 2; and/or

(b) a heavy chain variable region (VH) comprising:

(i) one, two or all of (e.g., three) a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2) and a heavy chain complementarity determining region 3 (HC CDR3) of a humanized B-H heavy chain (HC) of Table 2; and

(ii) a framework region (FR) having at least 95% identity with one, two, three or all (e.g., four) of a framework region 1 (FR1), a framework region 2 (FR2), a framework region 3 (FR3), and a framework region 4 (FR4) of a humanized B-H HC of Table 2.

In some embodiments, the anti-TCRBV binds to TCRβV12, e.g., TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01, or a variant thereof.

In some embodiment, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a HC CDR1, a HC CDR2 and a HC CDR3 of Antibody B listed in Table 2; or

(ii) a LC CDR1, a LC CDR2, and a LC CDR3 of Antibody B listed in Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a light chain variable region (VL) comprising one, two or all (e.g., three) of a LC CDR1, a LC CDR2 and a LC CDR3 of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11, or an amino acid sequence listed in Table 1.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a heavy chain variable region (VH) comprising one, two or all (e.g., three) of a HC CDR1, a HC CDR2 and a HC CDR3 of a humanized B-H antibody listed in Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a light chain variable region (VL) comprising one, two or all (e.g., three) of a LC CDR1, a LC CDR2 and a LC CDR3 of a humanized B-H antibody listed in Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises:

a VH sequence of a humanized B-H antibody listed in Table 2, or a sequence having at least about 85%, 90%, 95%, or 99% sequence identity to a VH of a humanized B-H antibody listed in Table 2; and/or

a VL sequence of a humanized B-H antibody listed in Table 2, or a sequence having at least about 85%, 90%, 95%, or 99% sequence identity to a VL of a humanized B-H antibody listed in Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with one of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H LC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with any two of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H LC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with any three of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H LC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with all of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H LC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with one of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H HC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with any two of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H HC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with any three of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H HC of Table 2.

In some embodiments, the anti-TCRβV antibody molecule comprises a framework region (FR) having at least 95% identity with all of: a FR1, a FR2, a FR3, and a FR4 of a humanized B-H HC of Table 2.

In another aspect, the disclosure provides a non-murine, e.g., a human-like antibody molecule (e.g., a human or humanized antibody molecule), which binds, e.g., specifically binds, to a T cell receptor beta variable (TCRβV) region. In some embodiments, binding of the anti-TCRβV antibody molecule results in expansion, e.g., at least about 1.1-50 fold expansion (e.g., at least about 1.5-40 fold, 2-35 fold, 3-30 fold, 5-25 fold, 8-20 fold, or 10-15 fold expansion), of a population of memory T cells, e.g., T effector memory (T_{EM}) cells, e.g., T_{EM} cells expressing CD45RA (T_{EMRA}) cells, e.g., CD4+ or CD8+T_{EMRA} cells. In some embodiments, the expansion is at least about 1.1-10 fold expansion (e.g., at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold expansion).

In some embodiments, expansion of the population of memory effector T cells, e.g., T_{EM} cells, e.g., T_{EMRA} cells, e.g., CD4+ or CD8+T_{EMRA} cells, is compared to expansion of a similar population of cells with an antibody that binds to: a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments, the population of expanded T effector memory cells comprises cells T cells, e.g., CD3+, CD8+ or CD4+ T cells. In some embodiments, the population of expanded T effector memory cells comprises CD3+ and CD8+ T cells. In some embodiments, the population of expanded T effector memory cells comprises CD3+ and CD4+ T cells.

In some embodiments, the population of expanded T effector memory (T_{EM}) cells comprises cells T cells, e.g., CD3+, CD8+ or CD4+ T cells, which express or re-express, CD45RA, e.g., CD45RA+. In some embodiments, the population comprises T_{EM} cells expressing CD45RA, e.g., T_{EMRA} cells. In some embodiments, expression of CD45RA on T_{EMRA} cells, e.g., CD4+ or CD8+T_{EMRA} cells, can be detected by a method disclosed herein, e.g., flow cytometry.

In some embodiments, T_{EMRA} cells have low or no expression of CCR7, e.g., CCR7- or CCR7 low. In some embodiments, expression of CCR7 on T_{EMRA} cells cannot be detected by a method disclosed herein, e.g., flow cytometry.

In some embodiments, T_{EMRA} cells express CD95, e.g., CD95+. In some embodiments, expression of CD95 on T_{EMRA} cells can be detected by a method disclosed herein, e.g., flow cytometry.

In some embodiments, T_{EMRA} cells express CD45RA, e.g., CD45RA+, have low or no expression of CCR7, e.g., CCR7- or CCR7 low, and express CD95, e.g., CD95+. In some embodiments T_{EMRA} cells can be identified as CD45RA+, CCR7- and CD95+ cells. In some embodiments, T_{EMRA} cells comprise CD3+, CD4+ or CD8+ T cells (e.g., CD3+ T cells, CD3+CD8+ T cells, or CD3+CD4+ T cells).

In some embodiments, binding of the anti-TCRβV antibody molecule results in expansion, e.g., at least about 1.1-50 fold expansion (e.g., at least about 1.5-40 fold, 2-35 fold, 3-30 fold, 5-25 fold, 8-20 fold, or 10-15 fold expansion), of a subpopulation of T cells. In some embodiments, the anti-TCRβV antibody molecule-activated (e.g., expanded) subpopulation of T cells resemble T_{EMRA} cells in high expression of CD45RA and/or low expression of CCR7. In some embodiments, the anti-TCRβV antibody molecule-activated (e.g., expanded) subpopulation of T cells do not display upregulation of the senescence markers CD57 and/or KLRG1. In some embodiments, the anti-TCRβV antibody molecule-activated (e.g., expanded) subpopulation of T cells do not display upregulation of co-stimulatory molecules CD27 and/or CD28. In some embodiments, the anti-TCRβV antibody molecule-activated (e.g., expanded) subpopulation of T cells are highly proliferative. In some embodiments, the anti-TCRβV antibody molecule-activated (e.g., expanded) subpopulation of T cells secrete IL-2. In some embodiments, expression of surface markers on T cells can be detected by a method disclosed herein, e.g., flow cytometry. In some embodiments, the proliferative capability of T cells can be detected by a method disclosed herein, e.g., a method described in Example 4. In some embodiments, cytokine expression of T cells can be detected by a method disclosed herein, e.g., a method described in Examples 10 and 21. In some embodiments, the expansion is at least about 1.1-10 fold expansion (e.g., at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold expansion). In some embodiments, the expansion is compared to expansion of a similar population of cells with an antibody that binds to a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments, binding of the anti-TCRβV antibody molecule to a TCRβV region results in one, two, three, four, five, six, seven, eight, nine, ten or more (e.g., all) of the following:

(i) reduced level, e.g., expression level, and/or activity of IL-1β;

(ii) reduced level, e.g., expression level, and/or activity of IL-6;

(iii) reduced level, e.g., expression level, and/or activity of TNFα;

(iv) increased level, e.g., expression level, and/or activity of IL-2;

(v) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours delay, in increased level, e.g., expression level, and/or activity of IL-2;

(vi) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours delay, in increased level, e.g., expression level, and/or activity of IFNg;

(vii) reduced T cell proliferation kinetics;

(viii) reduced cytokine storm, e.g., cytokine release syndrome (CRS) and/or neurotoxicity (NT), e.g., as measured by an assay of Example 3;

(ix) cell killing, e.g., target cell killing, e.g. cancer cell killing, e.g., as measured by an assay of Example 4;

(x) increased level, e.g., expression level, and/or activity of IL-15; or

(xi) increased Natural Killer (NK) cell proliferation, e.g., expansion, compared to an antibody that binds to: a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a reduction of at least 2, 5, 10, 20, 50, 100, or 200 fold, or at least 2-200 fold (e.g., 5-150, 10-100, 20-50 fold) in the expression level and or activity of IL-1β as measured by an assay of Example 3.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a reduction of at least 2, 5, 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 fold, or at least 2-1000 fold (e.g., 5-900, 10-800, 20-700, 50-600, 100-500, or 200-400 fold) in the expression level and or activity of IL-6 as measured by an assay of Example 3.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a reduction of at least 2, 5, 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, or 2000 fold, or at least 2-2000 fold (e.g., 5-1000, 10-900, 20-800, 50-700, 100-600, 200-500, or 300-400 fold) in the expression level and or activity of TNFα as measured by an assay of Example 3.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in an increase of at least 2, 5, 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, or 2000 fold, or at least 2-2000 fold (e.g., 5-1000, 10-900, 20-800, 50-700, 100-600, 200-500, or 300-400 fold) in the expression level and or activity of IL-2 as measured by an assay of Example 3.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in an increase of at least 2, 5, 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, or 2000 fold, or at least 2-2000 fold (e.g., 5-1000, 10-900, 20-800, 50-700, 100-600, 200-500, or 300-400 fold) in the expression level and or activity of IL-15 as measured by an assay of Example 4.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule results in proliferation, e.g., expansion, e.g., at least about 1.1-50 fold expansion (e.g., at least about 1.5-40 fold, 2-35 fold, 3-30 fold, 5-25 fold, 8-20 fold, or 10-15 fold expansion), of a population of Natural Killer (NK) cells. In some embodiments, the expansion of NK cells is at least about 1.1-30 fold expansion (e.g., at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, or at least about 1.1-5, 5-10, 10-15, 15-20, 20-25, or 25-30 fold expansion). In some embodiments, the expansion of NK cells is measure by an assay of Example 4. In some embodiments, the expansion of NK cells by, e.g., binding of, the anti-TCRβV antibody molecule is compared to expansion of an otherwise similar population not contacted with the anti-TCRβV antibody molecule.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody mol-

ecule results in cell killing, e.g., target cell killing, e.g. cancer cell killing. In some embodiments, the cancer cell is a hematological cancer cell or a solid tumor cell. In some embodiments, the cancer cell is a multiple myeloma cell. In some embodiments, binding of the anti-TCRβV antibody molecule results in cell killing in vitro or in vivo. In some embodiments, cell killing is measured by an assay of Example 4.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in an increase or decrease of at least 2, 5, 10, 20, 50, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, or 2000 fold, or at least 2-2000 fold (e.g., 5-1000, 10-900, 20-800, 50-700, 100-600, 200-500, or 300-400 fold) of any of the activities described herein compared the activity of 16G8 or TM23 murine antibody, or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In an aspect, provided herein is an antibody molecule which binds, e.g., specifically binds, to a T cell receptor beta variable chain (TCRβV) region (an anti-TCRβV antibody molecule), wherein the anti-TCRβV antibody molecule:

(i) binds specifically to an epitope on TCRβV, e.g., the same or similar epitope as the epitope recognized by an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(ii) shows the same or similar binding affinity or specificity, or both, as an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(iii) inhibits, e.g., competitively inhibits, the binding of an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(iv) binds the same or an overlapping epitope with an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule; or

(v) competes for binding, and/or binds the same epitope, with an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule,

In some embodiments, the second anti-TCRβV antibody molecule comprises an antigen binding domain chosen from Table 1 or Table 2, or a sequence substantially identical thereto. In some embodiments, the second anti-TCRβV antibody molecule comprises an antigen binding domain, comprising:

a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2) and/or a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1 or SEQ ID NO: 9; and/or a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and/or a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11.

In some embodiments of any of the compositions disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a change in any (e.g., one, two, three, four or all) of (i)-(v) that is different, e.g., an increase or decrease, of at least 2, 5, 10, 20, 50, 100-fold, compared the activity of 16G8 or TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to a TCRBV family (e.g., gene family), e.g., a TCRBV gene family comprising subfamilies, e.g., as described herein. In some embodiments, the TCRBV family, e.g., gene family, comprises: a TCRβV6 subfamily, a TCRβV10 subfamily, a TCRβV12 subfamily, a TCRβV5 subfamily, a TCRβV7 subfamily, a TCRβV11 subfamily, a TCRβV14 subfamily, a TCRβV16 subfamily, a TCRβV18 subfamily, a TCRβV9 subfamily, a TCRβV13 subfamily, a TCRβV4 subfamily, a TCRβV3 subfamily, a TCRβV2 subfamily, a TCRβV15 v, a TCRβV30 subfamily, a TCRβV19 subfamily, a TCRβV27 subfamily, a TCRβV28 subfamily, a TCRβV24 subfamily, a TCRβV20 subfamily, TCRβV25 subfamily, a TCRβV29 subfamily, a TCRβV23 subfamily, a TCRβV21 subfamily, a TCRβV1 subfamily, a TCRβV17 subfamily, or a TCRβV26 subfamily.

In some embodiments, the anti-TCRβV antibody binds to a TCRβV6 subfamily chosen from: TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments the TCRβV6 subfamily comprises TCRβV6-5*01.

In some embodiments, the anti-TCRβV antibody binds to a TCRβV10 subfamily chosen from: TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01.

In some embodiments, the anti-TCRβV antibody binds to a TCRβV12 subfamily chosen from: TCRβV12-4*01, TCRβV12-3*01 or TCRβV12-5*01.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not bind to TCRβV12, or binds to TCRβV12 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV12 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV12 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not comprise at least one CDR of Antibody B. In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not comprise the CDRs of Antibody B.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody binds to a TCRβV5 subfamily chosen from: TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody binds to a TCRβV5 subfamily chosen from: TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01, or binds to

TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV5-5*01 or TCRβV5-1*01 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not comprise at least one CDR of the TM23 murine antibody. In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule does not comprise the CDRs of the TM23 murine antibody.

In some embodiments of any of the compositions disclosed herein, an anti-TCRβV antibody molecule disclosed herein does not comprise the sequence of a murine anti-rat TCR antibody R73, e.g., as disclosed in J Exp Med. 1989 Jan. 1; 169(1): 73-86, herein incorporated by reference in its entirety. In some embodiments of any of the compositions disclosed herein, a multispecific antibody molecule disclosed herein does not comprise the sequence of a murine anti-rat TCR antibody R73, e.g., as disclosed in J Immunol. 1993 Mar. 15; 150(6):2305-15, herein incorporated by reference in its entirety.

In some embodiments of any of the compositions disclosed herein, an anti-TCRβV antibody molecule disclosed herein does not comprise a viral peptide-WIC complex, e.g., as disclosed in Oncoimmunology. 2016; 5(1): e1052930, herein incorporated by reference in its entirety. In some embodiments of any of the compositions disclosed herein, a multispecific antibody molecule disclosed herein does not comprise a viral peptide-WIC complex, e.g., as disclosed in Oncoimmunology. 2016; 5(1): e1052930, herein incorporated by reference in its entirety.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to one or more (e.g., all) of the following TCRβV subfamilies:

(i) TCRβV6 subfamily comprising, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01;

(ii) TCRβV10 subfamily comprising, e.g., one or more of TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01;

(iii) TCRβV5 subfamily comprising, e.g., one or more of TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01;

(iv) TCRβV12 subfamily comprising e.g., one or more of TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01;

(v) TCRβV7 subfamily comprising e.g., one or more of TCRβV7-7*01, TCRβV7-6*01, TCRβV7-8*02, TCRβV7-4*01, TCRβV7-2*02, TCRβV7-2*03, TCRβV7-2*01, TCRβ V7-3*01, TCRβV7-9*03, or TCRβV7-9*01;

(vi) TCRβV11 subfamily comprising e.g., one or more of TCRβV11-1*01, TCRβV11-2*01 or TCRβV11-3*01;

(vii) TCRβV14 subfamily comprising TCRβV14*01;

(viii) TCRβV16 subfamily comprising TCRβV16*01;

(ix) TCRβV18 subfamily comprising TCRβV18*01;

(x) TCRβV9 subfamily comprising T e.g., one or more of CRβV9*01 or TCRβV9*02;

(xi) TCRβV13 subfamily comprising TCRβV13*01;

(xii) TCRβV4 subfamily comprising e.g., one or more of e.g., one or more of TCRβV4-2*01, TCRβV4-3*01, or TCRβV4-1*01;

(xiii) TCRβV3 subfamily comprising TCRβV3-1*01;

(xiv) TCRβV2 subfamily comprising TCRβV2*01;

(xv) TCRβV15 subfamily comprising TCRβV15*01;

(xvi) TCRβV30 subfamily comprising e.g., one or more of TCRβV30*01, or TCRβV30*02;

(xvii) TCRβV19 subfamily comprising e.g., one or more of TCRβV19*01, or TCRβV19*02;

(xviii) TCRβV27 subfamily comprising TCRβV27*01;

(xix) TCRβV28 subfamily comprising TCRβV28*01;

(xx) TCRβV24 subfamily comprising TCRβV24-1*01;

(xxi) TCRβV20 subfamily comprising e.g., one or more of TCRβV20-1*01, or TCRβV20-1*02;

(xxii) TCRβV25 subfamily comprising TCRβV25-1*01; or

(xxiii) TCRβV29 subfamily comprising TCRβV29-1*01;

(xxiv) TCRβV21 subfamily;

(xxv) TCRβV1 subfamily;

(xxvi) TCRβV17 subfamily;

(xvii) TCRβV23 subfamily; or

(xviii) TCRβV26 subfamily.

In some embodiments of any of the compositions disclosed herein, the anti-TCRβV antibody molecule binds to one or more (e.g., all) of the following TCRβV subfamilies:

(i) TCRβV6, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01;

(ii) TCRβV10, e.g., one or more of TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01;

(iii) TCRβV12, e.g., one or more of TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01; or

(iv) TCRβV5, e.g., one or more of TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV6, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV6-5*01.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV12.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01.

In an aspect, provided herein is a multispecific molecule (e.g., a bispecific molecule), comprising a first moiety (e.g., a first immune cell engager) comprising an antibody molecule which binds (e.g., specifically binds) to a T cell receptor beta variable region (TCRβV) ("anti-TCRβV antibody molecule").

In some embodiments, the multispecific molecule comprises a second moiety which comprises one or more of: a tumor-targeting moiety, a cytokine molecule, a stromal modifying moiety, or an anti-TCRβV antibody molecule other than the first moiety.

In some embodiments, binding of the first moiety to the TCRβV region results in a cytokine profile, e.g., cytokine secretion profile, that differs from that of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager").

In another aspect, the disclosure provides a multispecific molecule, e.g., a bispecific molecule, comprising the anti-TCRβV antibody molecule disclosed herein.

In some embodiments, the multispecific molecule further comprises: a tumor-targeting moiety, a cytokine molecule, an immune cell engager, e.g., a second immune cell engager, and/or a stromal modifying moiety.

In yet another aspect, disclosed herein is a multispecific molecule, e.g., a bispecific molecule, comprising:

(i) a first moiety comprising a first immune cell engager comprising an anti-TCRβV antibody molecule disclosed herein; and

(ii) a second moiety comprising one or more of: a tumor-targeting moiety; a second immune cell engager; a cytokine molecule or a stromal modifying moiety.

In another aspect, the disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding an anti-TCRβV antibody molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto.

In another aspect, the disclosure provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a multispecific molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto.

In yet another aspect, the disclosure provides a vector, e.g., an expression vector, comprising a nucleotide sequence encoding an anti-TCRβV antibody molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto.

In another aspect, the disclosure provides a vector, e.g., an expression vector, comprising a nucleotide sequence encoding a multispecific molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto.

In one aspect, the disclosure provides a cell, e.g., host cell, e.g., a population of cells, comprising a nucleic acid molecule encoding an anti-TCRβV antibody molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto. In some embodiments, the cell or population of cells comprising a nucleic acid molecule encoding anti-TCRβV antibody molecule, comprises: (i) a heavy chain comprising: a variable region (VH), e.g., a VH listed in Table 1 or 2, or a sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto; and one or more heavy chain constant regions, e.g., as described herein; and/or (ii) a light chain comprising: a variable region (VL) e.g., a VL listed in Table 1 or 2, or a sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto; and a light chain constant region, e.g., as described herein, e.g., a kappa chain constant region comprising the sequence of SEQ ID NO: 39, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the cell or population of cells further comprises an IgJ heavy chain constant region or a fragment thereof. In some embodiments, the IgJ heavy chain constant region comprises the sequence of SEQ ID NO: 76 or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, the IgJ is comprised in, e.g., expressed in, the same cell or population of cells comprising, e.g., expressing, the anti-TCRβV antibody molecule, e.g., the heavy chain and/or the light chain of the anti-TCRβV antibody molecule. In some embodiments, the IgJ is expressed in a different cell or population of cells than the cell or population of cells comprising, e.g., expressing, the anti-TCRβV antibody molecule, e.g., the heavy chain and/or the light chain of the anti-TCRβV antibody molecule.

In one aspect, the disclosure provides a cell, e.g., host cell, e.g., a population of cells, comprising a nucleic acid molecule encoding a multispecific molecule disclosed herein, or a nucleotide sequence having at least 75%, 80%, 85%, 90%, 95%, or 99% identity thereto.

In one aspect, disclosed herein is an anti-TCRβV antibody molecule for use in the manufacture of a medicament for treating a disease, e.g., cancer, in a subject.

In one aspect, disclosed herein is a multispecific molecule comprising an anti-TCRβV antibody molecule for use in the manufacture of a medicament for treating a disease, e.g., cancer, in a subject.

In another aspect, the disclosure provides a method of making, e.g., producing, an anti-TCRβV antibody molecule, a multispecific molecule described herein, comprising culturing a host cell described herein, under suitable conditions. In some embodiments of a method of making a multispecific molecule, the conditions comprise, e.g., conditions suitable for gene expression and/or homo- or heterodimerization.

In another aspect, the disclosure provides a pharmaceutical composition comprising an anti-TCRβV antibody molecule, or a multispecific molecule described herein, and a pharmaceutically acceptable carrier, excipient, or stabilizer.

In an aspect, the disclosure provides a method of modulating, e.g., enhancing, an immune response in a subject comprising administering to the subject an effective amount of an antibody molecule which binds (e.g., specifically binds) to a T cell receptor beta variable region (TCRβV) ("anti-TCRβV antibody molecule").

In an aspect, the disclosure provides a method of modulating, e.g., enhancing, an immune response in a subject comprising administering to the subject an effective amount of a multispecific molecule disclosed herein.

In some embodiments, the method comprises expanding, e.g., increasing the number of, an immune cell population in the subject.

In an aspect, the disclosure provides a method of expanding, e.g., increasing the number of, an immune cell population comprising, contacting the immune cell population with an effective amount of an antibody molecule which binds (e.g., specifically binds) to a T cell receptor beta variable region (TCRβV) ("anti-TCRβV antibody molecule").

In an aspect, the disclosure provides a method of expanding, e.g., increasing the number of, an immune cell population comprising, contacting the immune cell population with an effective amount of a multispecific molecule disclosed herein.

In some embodiments, the expansion occurs in vivo or ex vivo (e.g., in vitro).

In some embodiments, the immune cell population comprises a TCRβV expressing cell, e.g., a TCRβV+ cell.

In some embodiments, the TCRβV expressing cell is a T cell, e.g., a CD8+ T cell, a CD3+ T cell or a CD4+ T cell.

In some embodiments, the immune cell population comprises a T cell (e.g., a CD4 T cell, a CD8 T cell, (e.g., an

effector T cell or a memory T cell (e.g., a memory effector T cell (e.g., TEM cell, e.g., TEMRA cell), or a tumor infiltrating lymphocyte (TIL).

In some embodiments, the immune cell population comprises a T cell, a Natural Killer cell, a B cell, or a myeloid cell.

In some embodiments, the immune cell population is obtained from a healthy subject.

In an aspect, provided herein is a method of treating a disease e.g., cancer, in a subject comprising administering to the subject an effective amount, e.g., a therapeutically effective amount, of an anti-TCRβV antibody molecule or a multispecific molecule comprising an anti-TCRβT antibody molecule disclosed herein, thereby treating the disease.

In a related aspect, provided herein is a composition comprising an anti-TCRβV antibody molecule or a multispecific molecule comprising an anti-TCRβV antibody molecule disclosed herein, for use in the treatment of a disease, e.g., cancer, in a subject.

In some embodiments, the disease is a cancer, e.g., a solid tumor or a hematological cancer, or a metastatic lesion.

In some embodiments, the method further comprises administering a second agent, e.g., therapeutic agent, e.g., as described herein. In some embodiments, second agent comprises a therapeutic agent (e.g., a chemotherapeutic agent, a biologic agent, hormonal therapy), radiation, or surgery. In some embodiments, therapeutic agent is selected from: a chemotherapeutic agent, or a biologic agent.

In another aspect, provided herein is a method of targeting, e.g., directing or re-directing, a therapy, e.g., treatment, to a T cell, e.g., in a subject, e.g., having a disease, e.g., cancer, comprising administering an effective amount of: (i) an anti-TCRβV antibody disclosed herein; and (ii) the therapy, e.g., a tumor targeting therapy (e.g., an antibody that binds to a cancer antigen), e.g., as described herein, thereby targeting the T cell.

In some embodiments, (i) and (ii) are conjugated, e.g., linked.

In some embodiments, (i) and (ii) are administered simultaneously or concurrently.

In some embodiments, the method results in: reduced cytokine release syndrome (CRS) (e.g., lesser duration of CRS or no CRS), or a reduced severity of CRS (e.g., absence of severe CRS, e.g., CRS grade 4 or 5) compared to administration of (ii) alone. In some embodiments, CRS is assessed by an assay of Example 3. In some embodiments, the method results in: reduced neurotoxicity (NT) (e.g., lesser duration of NT or no NT), or a reduced severity of NT (e.g., absence of severe NT) compared to administration of (ii) alone.

In yet another aspect, the disclosure provides, a method of targeting a T cell, e.g., in a subject having a disease, e.g., cancer, with an anti-TCRβV antibody disclosed herein or a multispecific molecule comprising an anti-TCRβV antibody disclosed herein.

In another aspect, the disclosure provides a method of treating, e.g., preventing or reducing, cytokine release syndrome (CRS) and/or neurotoxicity (NT) in a subject, e.g., CRS and/or NT associated with a treatment, e.g., a previously administered treatment, comprising administering to the subject an effective amount of an anti-TCRβV antibody disclosed herein or a multispecific molecule comprising an anti-TCRβV antibody disclosed herein, wherein, the subject has a disease, e.g., a cancer, thereby treating, e.g., preventing or reducing, CRS and/or NT in the subject.

In a related aspect, the disclosure provides a composition comprising an anti-TCRβV antibody disclosed herein or a multispecific molecule comprising an anti-TCRβV antibody disclosed herein, for use in the treatment, e.g., prevention or reduction, of cytokine release syndrome (CRS) and/or neurotoxicity (NT) in a subject, e.g., CRS and/or NT associated with a treatment, e.g., a previously administered treatment, comprising administering to the subject an effective amount of the anti-TCRβV antibody, wherein the subject has a disease, e.g., a cancer.

In some embodiments of a method or composition for use disclosed herein, the anti-TCRβV antibody is administered concurrently with or after the administration of the treatment associated with CRS and/or NT.

In another aspect, provided herein is a method of expanding, e.g., increasing the number of, an immune cell population comprising, contacting the immune cell population with an antibody molecule, e.g., humanized antibody molecule, which binds, e.g., specifically binds, to a T cell receptor beta variable chain (TCRβV) region (e.g., anti-TCRβV antibody molecule described herein or a multispecific molecule comprising an anti-TCRβV antibody molecule described herein), thereby expanding the immune cell population.

In some embodiments, the expansion occurs in vivo or ex vivo (e.g., in vitro).

In an aspect, provided herein is a method of evaluating a subject having a cancer, comprising acquiring a value of the status of a TCRβV molecule for the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject, wherein the value of the status of a TCRβV molecule is higher, e.g., increased, in a sample from the subject compared to a reference value, e.g., a value from a healthy subject, e.g., a subject that does not have cancer.

In another aspect, the disclosure provides a method of treating a subject having a cancer, the method comprising (i) acquiring a value of the status of a TCRβV molecule for the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβW molecule in a sample from the subject, and (ii) responsive to said value, administering an effective amount of an anti-TCRβV antibody molecule described herein (e.g., a TCRβV agonist) to the subject, thereby treating the cancer.

In some embodiments, the value is higher, e.g., increased, in a sample from the subject compared to a reference value, e.g., a value from a healthy subject, e.g., a subject that does not have cancer.

In a related aspect, the disclosure provides a composition comprising an anti-TCRβV antibody molecule for use in the treatment of a subject having a cancer, comprising (i) acquiring a value of the status of a TCRβV molecule for the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject, and (ii) responsive to said value, administering an effective amount of an anti-TCRβV antibody molecule described herein (e.g., a TCRβV agonist) to the subject.

In an aspect, provided herein is method of evaluating a subject for the presence of a cancer, the method comprising:

(i) acquiring a value of the status of one or more TCRβV molecules for the subject, e.g., in a biological sample from the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject, and

(ii) determining whether the value for the one or more TCRβV molecules is higher, e.g., increased, in a sample from the subject compared to a reference value, e.g., a value from a healthy subject, e.g., a subject that

does not have cancer, wherein a value that is higher, e.g., increased, in the subject relative to the reference, e.g., healthy subject, is indicative of the presence of cancer in the subject.

In another aspect, the disclosure provides, a method of treating a subject having cancer, the method comprising:

(i) acquiring a value of the status of one or more TCRβV molecules for the subject, e.g., in a biological sample from the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject;

(ii) determining whether the value for the one or more TCRβV molecules is higher, e.g., increased, in a sample from the subject compared to a reference value, e.g., a value from a healthy subject, e.g., a subject that does not have cancer, and

(iii) if a value that is higher, e.g., increased, in the subject relative to the reference value is determined, administering an effective amount of an anti-TCRβV antibody molecule, e.g., as described herein (e.g., a TCRβV agonist), to the subject, thereby treating the cancer.

In a related aspect, provided herein is a composition comprising anti-TCRβV antibody molecule for use in a method of treating a subject having a cancer, comprising

(i) acquiring a value of the status of one or more TCRβV molecules for the subject, e.g., in a biological sample from the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject;

(ii) determining whether the value for the one or more TCRβV molecules is higher, e.g., increased, in a sample from the subject compared to a reference value, e.g., a value from a healthy subject, e.g., a subject that does not have cancer, and

(iii) if a value that is higher, e.g., increased, in the subject relative to the reference value is determined, administering an effective amount of an anti-TCRβV antibody molecule, e.g., as described herein (e.g., a TCRβV agonist), to the subject.

In some embodiments of any of the methods of treatment, or composition for use disclosed herein, the status is indicative of the subject having cancer, or a symptom thereof.

In some embodiments of any of the methods of treatment or composition for use disclosed herein, the status is indicative of responsiveness to a therapy, e.g., a therapy comprising an anti-TCRβV antibody molecule, e.g., as described herein.

In some embodiments of any of the methods of treatment or composition for use disclosed herein, the value of the status is determined, e.g., measured, by an assay described herein.

In yet another aspect, provided herein is a method of treating a subject having a cancer, comprising administering to the subject an effective amount of an anti-TCRBV antibody molecule described herein, wherein the subject has a higher, e.g., increased, level or activity of one or more TCRBV molecules, e.g., as described herein, compared to a reference level or activity of one or more TCRBV molecules, e.g., in a healthy subject, e.g., a subject not having a cancer

In an aspect, the disclosure provides, method of treating a subject having a cancer, comprising

(i) isolating a biological sample from the subject; e.g., a peripheral blood sample, biopsy sample, or bone marrow sample; and

(ii) acquiring a value of the status of one or more TCRβV molecules for the subject, e.g., in the biological sample from the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRBV molecule in a sample from the subject compared to a reference value, e.g., a sample from a health subject, wherein a value that is higher, e.g., increased, in the subject relative to the reference, e.g., healthy subject, is indicative of the presence of cancer in the subject,

(iii) contacting the biological sample with an anti-TCRβV antibody molecule, e.g., in vitro; and

(iv) administering the biological sample or a portion thereof from step (iii) to the subject.

In another aspect, provided herein is method of expanding a population of immune effector cells from a subject having a cancer, the method comprising:

(i) isolating a biological sample comprising a population of immune effector cells from the subject; e.g., a peripheral blood sample, biopsy sample, or bone marrow sample;

(ii) acquiring a value of the status of one or more TCRβV molecules for the subject, e.g., in the biological sample from the subject, wherein said value comprises a measure of the presence of, e.g., level or activity of, a TCRβV molecule in a sample from the subject compared to a reference value, e.g., a sample from a health subject, wherein a value that is higher, e.g., increased, in the subject relative to the reference, e.g., healthy subject, is indicative of the presence of cancer in the subject, and

(iii) contacting the biological sample comprising a population of immune effector cells with an anti-TCRβV antibody molecule.

In some embodiments, the method further comprises administering the population of immune effector cells contacted with the anti-TCRβV antibody molecule to the subject.

In some embodiments, a method of expansion, or method of treatment, or composition for use disclosed herein comprises measuring T cell function (e.g., cytotoxic activity, cytokine secretion, or degranulation) in the population of immune effector cells, e.g., compared to a reference population, e.g., an otherwise similar population not contacted with the anti-TCRβV antibody molecule or a population of immune effector cells obtained from a healthy subject (e.g., a subject that does not have a cancer).

In some embodiments of any of the methods or composition for use disclosed herein, the biological sample comprising the population of immune effector cells is contacted with an anti-TCRβV antibody molecule that binds to the one or more TCRβV molecules (e.g., the same TCRβV molecule) identified as being higher, e.g., increased, in the biological sample.

In some embodiments of any of the methods or composition for use disclosed herein, the biological sample comprising the population of immune effector cells is contacted with an anti-TCRβV antibody molecule that does not bind to the one or more TCRβV molecules (e.g., a different TCRβV molecule) identified as being higher, e.g., increased, in the biological sample.

In another aspect, provided herein is a method of identifying one or more TCRβV molecules associated with a cancer, the method comprising:

(i) acquiring a status for a plurality of TCRβV molecules in a biological sample from a first subject having the disease and in a biological sample from a second subject not having the disease; and

(ii) determining whether the level or activity of one or more of the TCRβV molecules is higher, e.g., increased, in the first subject relative to the second subject; thereby identifying one or more TCRβV molecules associated with the cancer.

In some embodiments of any of the methods or composition for use disclosed herein, the one or more of the TCRβV molecules comprises one or more, (e.g., all) of the following TCRβV subfamilies:

(i) TCRβV6 subfamily comprising, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01;

(ii) TCRβV10 subfamily comprising, e.g., one or more of TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01;

(iii) TCRβV5 subfamily comprising, e.g., one or more of TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01;

(iv) TCRβV12 subfamily comprising e.g., one or more of TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01;

(v) TCRβV7 subfamily comprising e.g., one or more of TCRβV7-7*01, TCRβV7-6*01, TCRβV7-8*02, TCRβV7-4*01, TCRβV7-2*02, TCRβV7-2*03, TCRβV7-2*01, TCRβ V7-3*01, TCRβV7-9*03, or TCRβV7-9*01;

(vi) TCRβV11 subfamily comprising e.g., one or more of TCRβV11-1*01, TCRβV11-2*01 or TCRβV11-3*01;

(vii) TCRβV14 subfamily comprising TCRβV14*01;

(viii) TCRβV16 subfamily comprising TCRβV16*01;

(ix) TCRβV18 subfamily comprising TCRβV18*01;

(x) TCRβV9 subfamily comprising T e.g., one or more of CRβ V9*01 or TCRβV9*02;

(xi) TCRβV13 subfamily comprising TCRβV13*01;

(xii) TCRβV4 subfamily comprising e.g., one or more of e.g., one or more of TCRβV4-2*01, TCRβV4-3*01, or TCRβV4-1*01;

(xiii) TCRβV3 subfamily comprising TCRβV3-1*01;

(xiv) TCRβV2 subfamily comprising TCRβV2*01;

(xv) TCRβV15 subfamily comprising TCRβV15*01;

(xvi) TCRβV30 subfamily comprising e.g., one or more of TCRβV30*01, or TCRβV30*02;

(xvii) TCRβV19 subfamily comprising e.g., one or more of TCRβV19*01, or TCRβV19*02;

(xviii) TCRβV27 subfamily comprising TCRβV27*01;

(xix) TCRβV28 subfamily comprising TCRβV28*01;

(xx) TCRβV24 subfamily comprising TCRβV24-1*01;

(xxi) TCRβV20 subfamily comprising e.g., one or more of TCRβV20-1*01, or TCRβV20-1*02;

(xxii) TCRβV25 subfamily comprising TCRβV25-1*01; or

(xxiii) TCRβV29 subfamily comprising TCRβV29-1*01;

(xxiv) TCRβV21 subfamily;

(xxv) TCRβV1 subfamily;

(xxvi) TCRβV17 subfamily;

(xvii) TCRβV23 subfamily; or

(xviii) TCRβV26 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the cancer is a solid tumor including but not limited to: melanoma, pancreatic (e.g., pancreatic adenocarcinoma) cancer, breast cancer, colorectal cancer (CRC), lung cancer (e.g., small or non-small cell lung cancer), skin cancer, ovarian cancer, or liver cancer.

In some embodiments of any of the methods or composition for use disclosed herein, the cancer is a hematological cancer including, but not limited to: a B-cell or T cell malignancy, e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma (e.g., B cell lymphoma, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia (B-CLL), mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, and acute lymphocytic leukemia.

In some embodiments of a method of expansion, or method of treatment, or composition for use disclosed herein, a higher, e.g., increased, level or activity of one or more TCRβV molecules in a subject, e.g., in a sample from a subject, is indicative of a bias, e.g., a preferential expansion, e.g., clonal expansion, of T cells expressing said one or more TCRβV molecules in the subject.

In some embodiments, a subject having a cancer, e.g., as disclosed herein, has a higher, e.g., increased, level or activity of one or more TCRβV molecules associated with the cancer. In some embodiments, the TCRβV molecule is associated with, e.g., recognizes, a cancer antigen, e.g., a cancer associated antigen or a neoantigen.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has B-CLL. In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01; (ii) TCRβV5 subfamily comprising TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01; (iii) TCRβV3 subfamily comprising TCRβV3-1*01; (iv) TCRβV2 subfamily comprising TCRβV2*01; or (v) TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV6 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV6 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV5 subfamily comprising TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV5 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV5 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV3 subfamily comprising TCRβV3-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV3 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV3 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV2 subfamily comprising TCRβV2*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV2 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV2 subfamily.

In some embodiments, a subject having B-CLL has a higher, e.g., increased, level or activity of a TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRBV molecule as described herein) that binds to one or more members of the TCRβV19 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV19 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has melanoma. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising the TCRβV6 subfamily comprising, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV6 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV6 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has DLBCL. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV13 subfamily comprising TCRβV13*01; (ii) TCRβV3 subfamily comprising TCRβV3-1*01; or (iii) TCRβV23 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV13 subfamily comprising TCRβV13*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV13 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV13 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV3 subfamily comprising TCRβV3-1*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV3 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV3 subfamily.

In some embodiments, a subject having DLBCL has a higher, e.g., increased, level or activity of a TCRβV23 subfamily. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV23 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV23 subfamily.

In some embodiments of any of the methods or composition for use disclosed herein, the subject has CRC. In some embodiments, a subject having melanoma has a higher, e.g., increased, level or activity of one or more TCRβV molecules, e.g., one or more TCRβV molecules comprising: (i) TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02; (ii) TCRβV12 subfamily comprising TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01; (iii) TCRβV16 subfamily comprising TCRβV16*01; or (iv) TCRβV21 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV19 subfamily comprising TCRβV19*01, or TCRβV19*02. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV19 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV19 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV12 subfamily comprising TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV12 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV12 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV16 subfamily comprising TCRβV16*01. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV16 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV16 subfamily.

In some embodiments, a subject having CRC has a higher, e.g., increased, level or activity of a TCRβV21 subfamily. In some embodiments, the subject is administered an anti-TCRβV molecule (e.g., an agonistic anti-TCRβV molecule as described herein) that binds to one or more members of the TCRβV21 subfamily. In some embodiments, administration of the an anti-TCRβV molecule results in expansion of immune cells expressing one or more members of the TCRβV21 subfamily.

Alternatively or in combination with any of the embodiments disclosed herein, provided herein is an anti-TCRβV antibody molecule which:

(i) binds specifically to an epitope on TCRβV, e.g., the same or similar epitope as the epitope recognized by an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(ii) shows the same or similar binding affinity or specificity, or both, as an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(iii) inhibits, e.g., competitively inhibits, the binding of an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule;

(iv) binds the same or an overlapping epitope with an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule; or

(v) competes for binding, and/or binds the same epitope, with an anti-TCRβV antibody molecule as described herein, e.g., a second anti-TCRβV antibody molecule,

In some embodiments, the second anti-TCRβV antibody molecule comprises an antigen binding domain chosen from Table 1 or Table 2, or a sequence substantially identical thereto. In some embodiments, the second anti-TCRβV antibody molecule comprises an antigen binding domain, comprising:

a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2) and/or a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1 or SEQ ID NO: 9; and/or a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and/or a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2) and/or a heavy chain complementarity determining region 3 (HC CDR3) of SEQ ID NO: 1 or SEQ ID NO: 9, or a sequence disclosed in Table 1; or

(ii) a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and/or a light chain complementarity determining region 3 (LC CDR3) of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11, or a sequence disclosed in Table 1.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a light chain variable region (VL) comprising one, two or all (e.g., three) of a LC CDR1, a LC CDR2 and a LC CDR3 of SEQ ID NO: 2, SEQ ID NO: 10 or SEQ ID NO: 11.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a heavy chain variable region (VH) comprising one, two or all (e.g., three) of a HC CDR1, a HC CDR2 and a HC CDR3 of SEQ ID NO:1 or SEQ ID NO: 9.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a VL comprising: a LC CDR1 amino acid sequence of SEQ ID NO: 6 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a LC CDR2 amino acid sequence of SEQ ID NO:7 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a LC CDR3 amino acid sequence of SEQ ID NO:8 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof); and/or

(ii) a VH comprising: a HC CDR1 amino acid sequence of SEQ ID NO: 3 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a HC CDR2 amino acid sequence of SEQ ID NO:4 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a HC CDR3 amino acid sequence of SEQ ID NO:5 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof).

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

a variable heavy chain (VH) of SEQ ID NO: 9, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto; and/or

a variable light chain (VL) of SEQ ID NO: 10 or SEQ ID NO: 11, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising the VH amino acid sequence of SEQ ID NO: 9 and the VL amino acid sequence of SEQ ID NO: 10.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising the VH amino acid sequence of SEQ ID NO: 9 and the VL amino acid sequence of SEQ ID NO: 11.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a heavy chain comprising a framework region, e.g., framework region 3 (FR3), comprising one or both of: (i) a Threonine at position 73, e.g., a substitution at position 73 according to Kabat numbering, e.g., a Glutamic Acid to Threonine substitution; or (ii) a Glycine at position, e.g., a substitution at position 94 according to Kabat numbering, e.g., a Arginine to Glycine substitution. In some embodiments, the substitution is relative to a human germline heavy chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising a Phenylalanine at position 10, e.g., a substitution at position 10 according to Kabat numbering, e.g., a Serine to Phenyalanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain comprising a framework region, e.g., framework region 2 (FR2), comprising one or both of: (i) a Histidine at position 36, e.g., a substitution at position 36 according to Kabat numbering, e.g., a Tyrosine to Histidine substitution; or (ii) an Alanine at position 46, e.g., a substitution at position 46 according to Kabat numbering, e.g., a Arginine to Alanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising a Phenylalanine at position 87, e.g., a substitution at position 87 according to Kabat numbering, e.g., a Tyrosine to Phenyalanine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments the anti-TCRβV antibody molecule binds to TCRβV6-5*01.

In some embodiments, TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01, is recognized, e.g., bound, by SEQ ID NO: 1 and/or SEQ ID NO: 2. In some embodiments, TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01, is recognized, e.g., bound, by SEQ ID NO: 9 and/or SEQ ID NO: 10. In some embodiments, TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01, is recognized, e.g., bound, by SEQ ID NO: 9 and/or SEQ ID NO: 11. In some embodiments, TCRβV6-5*01 is recognized, e.g., bound by SEQ ID NO: 9 and/or SEQ ID NO: 10, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments, TCRβV6-5*01 is recognized, e.g., bound by SEQ ID NO: 9 and/or SEQ ID NO: 11, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a heavy chain complementarity determining region (HC CDR1), a HC CDR2 and/or a HC CDR3 of SEQ ID NO: 15, SEQ ID NO: 23, SEQ ID NO: 24 or SEQ IC NO: 25, or a sequence disclosed in Table 2; and/or

(ii) a light chain complementarity determining region 1 (LC CDR1), a LC CDR2, and/or a LC CDR3 of SEQ ID NO: 16, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO:30, or a sequence disclosed in Table 2.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a light chain variable region (VL) comprising one, two or all of a LC CDR1, a LC CDR2 and a LC CDR3 of SEQ ID NO: 16, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO:30.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a heavy chain variable region (VH) comprising one, two or all of a HC CDR1, a HC CDR2 and a HC CDR3 of SEQ ID NO: 15, SEQ ID NO: 23, SEQ ID NO: 24 or SEQ ID NO: 25.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

(i) a VL comprising: a LC CDR1 amino acid sequence of SEQ ID NO: 20 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a LC CDR2 amino acid sequence of SEQ ID NO:21 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a LC CDR3 amino acid sequence of SEQ ID NO:22 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof); and/or

(ii) a VH comprising: a HC CDR1 amino acid sequence of SEQ ID NO: 17 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), a HC CDR2 amino acid sequence of SEQ ID NO:18 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof), and/or a HC CDR3 amino acid sequence of SEQ ID NO:19 (or an amino acid sequence with not more than 1, 2, 3 or 4 modifications, e.g., substitutions, additions or deletions thereof).

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises an antigen binding domain comprising:

a variable heavy chain (VH) of SEQ ID NO: 23, SEQ ID NO: 24 or SEQ ID NO: 25, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto; and/or

a variable light chain (VL) of SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29 or SEQ ID NO:30, or a sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain comprising a framework region, e.g., framework region 1 (FR1), comprising one, two or all (e.g., three) of: (i) an Aspartic Acid at position 1, e.g., a substitution at position 1 according to Kabat numbering, e.g., a Alanine to Aspartic Acid substitution; or (ii) an Asparagine at position 2, e.g., a substitution at position 2 according to Kabat numbering, e.g., a Isoleucine to Asparagine substitution, a Serine to Asparagine substitution, or a Tyrosine to Asparagine substitution; or (iii) a Leucine at position 4, e.g., a substitution at position 4 according to Kabat numbering, e.g., a Methionine to Leucine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain comprising a framework region, e.g., framework region 3 (FR3), comprising one, two or all (e.g., three) of: (i) a Glycine as position 66, e.g., a substitution at position 66 according to Kabat numbering, e.g., a Lysine to Glycine substitution, or a Serine to Glycine substitution; or (ii) an Asparagine at position 69, e.g., a substitution at position 69 according to Kabat numbering, e.g., a Threonine to Asparagine substitution; or (iii) a Tyrosine at position 71, e.g., a substitution at position 71 according to Kabat numbering, e.g., a Phenylalanine to Tyrosine substitution, or an Alanine to Tyrosine substitution. In some embodiments, the substitution is relative to a human germline light chain framework region sequence.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV12, e.g., TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01. In some embodiments the anti-TCRβV antibody molecule binds to TCRβV12-4*01 or TCRβV12-3*01.

In some embodiments, TCRβV12, e.g., TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01 is recognized, e.g., bound, by SEQ ID NO: 15 and/or SEQ ID NO: 16. In some embodiments, TCRβV12, e.g., TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01, is recognized, e.g., bound, by any one of SEQ ID NOs 23-25, and/or any one of SEQ ID NO:

26-30, or an amino acid sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments TCRβV12-4*01 is recognized, e.g., bound, by any one of SEQ ID NOs 23-25, and/or any one of SEQ ID NO: 26-30, or an amino acid sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments TCRβV12-3*01 is recognized, e.g., bound, by any one of SEQ ID NOs 23-25, and/or any one of SEQ ID NO: 26-30, or an amino acid sequence having at least about 75%, 80%, 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises the anti-TCRβV antibody molecule comprises an antigen binding domain comprising a single chain Fv (scFv) or a Fab.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises binds to a conformational or a linear epitope on the T cell.

In some embodiments of any of the compositions or methods disclosed herein, the tumor comprises an antigen, e.g., a tumor antigen, e.g., a tumor associated antigen or a neoantigen. In some embodiments, the anti-TCRβV antibody molecule recognize, e.g., bind to, the tumor antigen.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule is a full antibody (e.g., an antibody that includes at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains), or an antigen-binding fragment (e.g., a Fab, $F(ab')_2$, Fv, a single chain Fv fragment, a single domain antibody, a diabody (dAb), a bivalent antibody, or bispecific antibody or fragment thereof, a single domain variant thereof, a camelid antibody, or a rat-derived VH.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises the anti-TCRβV antibody molecule comprises one or more heavy chain constant regions chosen from IgG1, IgG2, IgG3, IgGA1, IgGA2, IgM, IgJ or IgG4, or a fragment thereof, e.g., as disclosed in Table 3.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a heavy chain constant region of an IgM or a fragment thereof, optionally wherein the IgM heavy chain constant region comprises the sequence of SEQ ID NO: 73, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto. In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprising an IgM constant region, further comprises a heavy chain constant region of an IgJ or a fragment thereof, optionally wherein the IgJ heavy chain constant region comprises the sequence of SEQ ID NO: 76 or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a heavy chain constant region of an IgJ or a fragment thereof, optionally wherein the IgJ heavy chain constant region comprises the sequence of SEQ ID NO: 76 or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a heavy chain constant region of an IgGA1, or a fragment thereof, optionally wherein the IgGA1 heavy chain constant region comprises the sequence of SEQ ID NO: 74, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a heavy chain constant region of an IgGA2, or a fragment thereof, optionally wherein the IgGA2 heavy chain constant region comprises a sequence listed in Table 3, e.g., SEQ ID NO: 75, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, binding of the anti-TCRβV antibody molecule to a TCRβV region results in a cytokine profile, e.g., a cytokine secretion profile, (e.g., comprising one or more cytokines and/or one or more chemokines), that differs from that of a T cell engager that binds to a receptor or molecule other than a TCRβV region ("a non-TCRβV-binding T cell engager").

In some embodiments, the cytokine profile, e.g., cytokine secretion profile, comprises the level and/or activity of one or more cytokines and/or one or more chemokines (e.g., as described herein). In an embodiment, a cytokine profile, e.g., a cytokine secretion profile, comprises the level and/or activity of one or more of: IL-2 (e.g., full length, a variant, or a fragment thereof); IL-1beta (e.g., full length, a variant, or a fragment thereof); IL-6 (e.g., full length, a variant, or a fragment thereof); TNFα (e.g., full length, a variant, or a fragment thereof); IFNg (e.g., full length, a variant, or a fragment thereof) IL-10 (e.g., full length, a variant, or a fragment thereof); IL-4 (e.g., full length, a variant, or a fragment thereof); TNF alpha (e.g., full length, a variant, or a fragment thereof); IL-12p70 (e.g., full length, a variant, or a fragment thereof); IL-13 (e.g., full length, a variant, or a fragment thereof); IL-8 (e.g., full length, a variant, or a fragment thereof); Eotaxin (e.g., full length, a variant, or a fragment thereof); Eotaxin-3 (e.g., full length, a variant, or a fragment thereof); IL-8 (HA) (e.g., full length, a variant, or a fragment thereof); IP-10 (e.g., full length, a variant, or a fragment thereof); MCP-1 (e.g., full length, a variant, or a fragment thereof); MCP-4 (e.g., full length, a variant, or a fragment thereof); MDC (e.g., full length, a variant, or a fragment thereof); MIP-1a (e.g., full length, a variant, or a fragment thereof); MIP-1b (e.g., full length, a variant, or a fragment thereof); TARC (e.g., full length, a variant, or a fragment thereof); GM-CSF (e.g., full length, a variant, or a fragment thereof); IL-12 23p40 (e.g., full length, a variant, or a fragment thereof); IL-15 (e.g., full length, a variant, or a fragment thereof); IL-16 (e.g., full length, a variant, or a fragment thereof); IL-17a (e.g., full length, a variant, or a fragment thereof); IL-1a (e.g., full length, a variant, or a fragment thereof); IL-5 (e.g., full length, a variant, or a fragment thereof); IL-7 (e.g., full length, a variant, or a fragment thereof); TNF-beta (e.g., full length, a variant, or a fragment thereof); or VEGF (e.g., full length, a variant, or a fragment thereof).

In some embodiments, the cytokine profile, e.g., cytokine secretion profile, comprises one, two, three, four, five, six, seven, or all of the following:

(i) increased level, e.g., expression level, and/or activity of IL-2;

(ii) reduced level, e.g., expression level, and/or activity of IL-1β;

(iii) reduced level, e.g., expression level, and/or activity of IL-6;

(iv) reduced level, e.g., expression level, and/or activity of TNFα;

(v) reduced level, e.g., expression level, and/or activity of IL-10;

(vi) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more hours delay, in increased level, e.g., expression level, and/or activity of IL-2;

(vii) a delay, e.g., at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hours delay, in increased level, e.g., expression level, and/or activity of IFNg; or

(viii) increased level, e.g., expression level, and/or activity of IL-15, e.g., wherein (i)-(viii) are relative to the cytokine profile, e.g., cytokine secretion profile, of the non-TCRβV-binding T cell engager.

In some embodiments, binding of the anti-TCRBV antibody to a TCRβV region results in reduced cytokine storm, e.g., reduced cytokine release syndrome (CRS) and/or neurotoxicity (NT), as measured by an assay of Example 3, e.g., relative to the cytokine storm induced by the non-TCRβV-binding T cell engager.

In some embodiments, binding of the anti-TCRBV antibody to a TCRβV region results in one, two, three or all of:

(ix) reduced T cell proliferation kinetics;

(x) cell killing, e.g., target cell killing, e.g. cancer cell killing, e.g., as measured by an assay of Example 4;

(xi) increased Natural Killer (NK) cell proliferation, e.g., expansion; or

(xii) expansion, e.g., at least about 1.1-10 fold expansion (e.g., at least about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold expansion), of a population of memory T cells, e.g., wherein (ix)-(xii) are relative to the non-TCRβV-binding T cell engager.

In some embodiments, an anti-TCRβV antibody molecule disclosed herein recognizes (e.g., binds to), a structurally conserved domain on the TCRβV protein (e.g., as denoted by the circled area in FIG. **24**A).

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, an interface of a TCRβV:TCRalpha complex.

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, a constant region of a TCRβV protein. An exemplary antibody that binds to a constant region of a TCRBV region is JOVI.1 as described in Viney et al., (*Hybridoma.* 1992 December; 11(6):701-13).

In some embodiments, an anti-TCRβV antibody molecule disclosed herein does not recognize, e.g., bind to, one or more (e.g., all) of a complementarity determining region (e.g., CDR1, CDR2 and/or CDR3) of a TCRβV protein.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain constant region chosen from the light chain constant regions of kappa or lambda, or a fragment thereof, e.g., as disclosed in Table 3.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises a light chain constant region of a kappa chain, or a fragment thereof, optionally wherein the kappa chain constant region comprises the sequence of SEQ ID NO: 39, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises:

(i) one or more heavy chain constant regions comprising a heavy chain constant region chosen from from IgG1, IgG2, IgG3, IgGA1, IgGA2, IgG4, IgJ, IgM, IgD, or IgE, or a fragment thereof, e.g., as described in Table 3; and

(ii) a light chain constant region comprising a light chain constant region chosen from the light chain constant regions of kappa or lambda, or a fragment thereof, e.g., as described in Table 3.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises or a cell comprising an anti-TCRβV antibody molecule comprises:

(i) a heavy chain comprising a variable region (VH), e.g., a VH of an antibody disclosed herein; and/or one or more heavy chain constant regions, e.g., as disclosed herein; and/or

(ii) a light chain comprising a variable light (VL), e.g., a VL of an antibody disclosed herein; and/or one or more light chain constant regions, e.g., as disclosed herein.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises, or a cell comprising an anti-TCRβV antibody molecule comprises:

(i) a heavy chain comprising a heavy chain constant region comprising:

(a) an IgM heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 73, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto;

(b) an IgGA1 heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 74, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; or

(c) an IgGA2 heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 75, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; and

(ii) a light chain comprising a light chain constant region comprising a kappa chain constant region comprising the sequence of SEQ ID NO: 39, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto,

optionally wherein, the anti-TCRβV antibody molecule further comprises an IgJ heavy chain constant region or a fragment thereof, wherein the IgJ heavy chain constant region comprises the sequence of SEQ ID NO: 76 or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the compositions or methods disclosed herein, the anti-TCRβV antibody molecule comprises, or a cell comprising an anti-TCRβV antibody molecule comprises:

(i) a heavy chain comprising: a VH chosen from a VH of Table 1 or 2, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; and a heavy chain constant region comprising:

(a) an IgM heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 73, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto;

(b) an IgGA1 heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 74, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; or

(c) an IgGA2 heavy chain constant region or a fragment thereof, comprising the sequence of SEQ ID NO: 75, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; and

(ii) a light chain comprising: a VL chosen from a VL of Table 1 or 2, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto; and a light

chain constant region comprising a kappa chain constant region comprising the sequence of SEQ ID NO: 39, or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto,

optionally wherein, the anti-TCRβV antibody molecule further comprises an IgJ heavy chain constant region or a fragment thereof, wherein the IgJ heavy chain constant region comprises the sequence of SEQ ID NO: 76 or a sequence with at least 85%, 90%, 95%, or 99% sequence identity thereto.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to one or more (e.g., all) of the following TCRβV subfamilies:

(i) TCRβV6 subfamily comprising, e.g., one or more of TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01;

(ii) TCRβV10 subfamily comprising, e.g., one or more of TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01;

(iii) TCRβV5 subfamily comprising, e.g., one or more of TCRβV5-6*01, TCRβV5-4*01, or TCRβV5-8*01;

(iv) TCRβV12 subfamily comprising e.g., one or more of TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01;

(v) TCRβV7 subfamily comprising e.g., one or more of TCRβV7-7*01, TCRβV7-6*01, TCRβV7-8*02, TCRβV7-4*01, TCRβV7-2*02, TCRβV7-2*03, TCRβV7-2*01, TCRβ V7-3*01, TCRβV7-9*03, or TCRβV7-9*01;

(vi) TCRβV11 subfamily comprising e.g., one or more of TCRβV11-1*01, TCRβV11-2*01 or TCRβV11-3*01;

(vii) TCRβV14 subfamily comprising TCRβV14*01;

(viii) TCRβV16 subfamily comprising TCRβV16*01;

(ix) TCRβV18 subfamily comprising TCRβV18*01;

(x) TCRβV9 subfamily comprising T e.g., one or more of CRβ V9*01 or TCRβV9*02;

(xi) TCRβV13 subfamily comprising TCRβV13*01;

(xii) TCRβV4 subfamily comprising e.g., one or more of e.g., one or more of TCRβV4-2*01, TCRβV4-3*01, or TCRβV4-1*01;

(xiii) TCRβV3 subfamily comprising TCRβV3-1*01;

(xiv) TCRβV2 subfamily comprising TCRβV2*01;

(xv) TCRβV15 subfamily comprising TCRβV15*01;

(xvi) TCRβV30 subfamily comprising e.g., one or more of TCRβV30*01, or TCRβV30*02;

(xvii) TCRβV19 subfamily comprising e.g., one or more of TCRβV19*01, or TCRβV19*02;

(xviii) TCRβV27 subfamily comprising TCRβV27*01;

(xix) TCRβV28 subfamily comprising TCRβV28*01;

(xx) TCRβV24 subfamily comprising TCRβV24-1*01;

(xxi) TCRβV20 subfamily comprising e.g., one or more of TCRβV20-1*01, or TCRβV20-1*02;

(xxii) TCRβV25 subfamily comprising TCRβV25-1*01; or

(xxiii) TCRβV29 subfamily comprising TCRβV29-1*01;

(xxiv) TCRβV21 subfamily;

(xxv) TCRβV1 subfamily;

(xxvi) TCRβV17 subfamily;

(xvii) TCRβV23 subfamily; or

(xviii) TCRβV26 subfamily.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to one or more (e.g., all) of the following TCRβV subfamilies:

(i) TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01;

(ii) TCRβV10, e.g., TCRβV10-1*01, TCRβV10-1*02, TCRβV10-3*01 or TCRβV10-2*01;

(iii) TCRβV12, e.g., TCRβV12-4*01, TCRβV12-3*01, or TCRβV12-5*01; or

(iv) TCRβV5, e.g., TCRβV5-5*01, TCRβV5-6*01, TCRβV5-4*01, TCRβV5-8*01, TCRβV5-1*01.

In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV6, e.g., TCRβV6-4*01, TCRβV6-4*02, TCRβV6-9*01, TCRβV6-8*01, TCRβV6-5*01, TCRβV6-6*02, TCRβV6-6*01, TCRβV6-2*01, TCRβV6-3*01 or TCRβV6-1*01. In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV6-5*01.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV12.

In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not bind to TCRβV12, or binds to TCRβV12 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV12 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV12 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not comprise at least one CDR of Antibody B. In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not comprise the CDRs of Antibody B.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01, or binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV5-5*01 or TCRβV5-1*01 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155.

In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not comprise at least one CDR of the TM23 murine antibody. In some embodiments of any of the methods disclosed herein, the anti-TCRβV antibody molecule does not comprise the CDRs of the TM23 murine antibody.

In some embodiments of any of the methods disclosed herein, an anti-TCRβV antibody molecule disclosed herein does not comprise the sequence of a murine anti-rat TCR antibody R73, e.g., as disclosed in J Exp Med. 1989 Jan. 1; 169(1): 73-86, herein incorporated by reference in its entirety. In some embodiments of any of the methods disclosed herein, a multispecific antibody molecule disclosed herein does not comprise the sequence of a murine anti-rat TCR antibody R73, e.g., as disclosed in J Immunol. 1993 Mar. 15; 150(6):2305-15, herein incorporated by reference in its entirety.

In some embodiments of any of the methods disclosed herein, an anti-TCRβV antibody molecule disclosed herein does not comprise a viral peptide-MHC complex, e.g., as disclosed in Oncoimmunology. 2016; 5(1): e1052930, herein incorporated by reference in its entirety. In some embodiments of any of the methods disclosed herein, a multispecific antibody molecule disclosed herein does not comprise a viral peptide-MHC complex, e.g., as disclosed in Oncoimmunology. 2016; 5(1): e1052930, herein incorporated by reference in its entirety.

In some embodiments of a method disclosed herein, the immune cell population comprises a T cell, a Natural Killer cell, a B cell, an antigen presenting cell, or a myeloid cell (e.g., a monocyte, a macrophage, a neutrophil or a granulocyte).

In some embodiments of a method disclosed herein, the immune cell population comprises a T cell, e.g., a CD4+ T cell, a CD8+ T cell, a TCR alpha-beta T cell, or a TCR gamma-delta T cell. In some embodiments, a T cell comprises a memory T cell (e.g., a central memory T cell, or an effector memory T cell (e.g., a T_{EMRA}) or an effector T cell. In some embodiments, a T cell comprises a tumor infiltrating lymphocyte (TIL).

In some embodiments of a method disclosed herein, the immune cell population is obtained from a healthy subject.

In some embodiments of a method disclosed herein, the immune cell population is obtained from a subject (e.g., from an apheresis sample from the subject) having a disease, e.g., a cancer, e.g., as described herein. In some embodiments, the immune cell population obtained from a subject having a disease, e.g., a cancer, comprises a tumor infiltrating lymphocyte (TIL).

In some embodiments of a method disclosed herein, the method results in an expansion of at least 1.1-10 fold (e.g., at least 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold expansion).

In some embodiments of a method disclosed herein, the method further comprises contacting the population of cells with an agent that promotes, e.g., increases, immune cell expansion. In some embodiments, the agent includes an immune checkpoint inhibitor, e.g., as described herein. In some embodiments, the agent includes a 4-1BB (CD127) agonist, e.g., an anti-4-1BB antibody.

In some embodiments of a method disclosed herein, the method further comprises comprising contacting the population of cells with a non-dividing population of cells, e.g., feeder cells, e.g., irradiated allogenic human PBMCs.

In some embodiments of a method disclosed herein, an expansion method described herein comprises expanding the cells for a period of at least about 4 hours, 6 hours, 10 hours, 12 hours, 15 hours, 18 hours, 20 hours, or 22 hours, or for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 1,6 17, 18, 19, 20 or 21 days, or for at least about 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks or 8 weeks.

In some embodiments of a method disclosed herein, expansion of the population of immune cells, is compared to expansion of a similar population of cells with an antibody that binds to: a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments of a method disclosed herein, expansion of the population of immune cells, is compared to expansion of a similar population of cells not contacted with the anti-TCRβV antibody molecule.

In some embodiments of a method disclosed herein, expansion of the population of memory effector T cells, e.g., T_{EM} cells, e.g., T_{EMRA} cells, is compared to expansion of a similar population of cells with an antibody that binds to: a CD3 molecule, e.g., CD3 epsilon (CD3e) molecule; or a TCR alpha (TCRα) molecule.

In some embodiments of a method disclosed herein, the method results in expansion of, e.g., selective or preferential expansion of, T cells expressing a T cell receptor (TCR) comprising a TCR alpha and/or TCR beta molecule, e.g., TCR alpha-beta T cells (αβ T cells).

In some embodiments of a method disclosed herein, the method results in expansion of αβ T cells over expansion of T cells expressing a TCR comprising a TCR gamma and/or TCR delta molecule, e.g., TCR gamma-delta T cells (γδ T cells). In some embodiments, expansion of αβ T cells over γδ T cells results in reduced production of cytokines associated with CRS. In some embodiments, expansion of αβ T cells over γδ T cells results in immune cells that have reduced capacity to, e.g., are less prone to, induce CRS upon administration into a subject.

In some embodiments of a method disclosed herein, an immune cell population (e.g., T cells (e.g., T_{EMRA} cells or TILs) or NK cells) cultured in the presence of, e.g., expanded with, an anti-TCRβV antibody disclosed herein does not induce CRS and/or NT when administered into a subject, e.g., a subject having a disease or condition as described herein.

In some embodiments, the anti-TCRβV antibody molecule in a multispecific molecule disclosed herein is a first immune cell engager moiety. In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV12, or binds to TCRβV12 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV12 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version

thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV12 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the 16G8 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule does not comprise the CDRs of the Antibody B murine antibody.

In some embodiments, the anti-TCRβV antibody molecule in a multispecific molecule disclosed herein is a first immune cell engager moiety. In some embodiments, the anti-TCRβV antibody molecule does not bind to TCRβV5-5*01 or TCRβV5-1*01, or binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is less than (e.g., less than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule binds to TCRβV5-5*01 or TCRβV5-1*01 with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule binds to a TCRβV region other than TCRβV5-5*01 or TCRβV5-1*01 (e.g., TCRβV region as described herein, e.g., TCRβV6 subfamily (e.g., TCRβV6-5*01) with an affinity and/or binding specificity that is greater than (e.g., greater than about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or about 2-, 5-, or 10-fold) the affinity and/or binding specificity of the TM23 murine antibody or a humanized version thereof as described in U.S. Pat. No. 5,861,155. In some embodiments, the anti-TCRβV antibody molecule does not comprise the CDRs of the TM23 murine antibody.

In some embodiments, the multispecific molecule further comprises a second immune cell engager moiety. In some embodiments, the first and/or second immune cell engager binds to and activates an immune cell, e.g., an effector cell. In some embodiments, the first and/or second immune cell engager binds to, but does not activate, an immune cell, e.g., an effector cell. In some embodiments, the second immune cell engager is chosen from an NK cell engager, a T cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager, or a combination thereof. In some embodiments, the second immune cell engager comprises a T cell engager which binds to CD3, TCRα, TCRγ, TCRζ, ICOS, CD28, CD27, HVEM, LIGHT, CD40, 4-1BB, OX40, DR3, GITR, CD30, TIM1, SLAM, CD2, or CD226.

In some embodiments, a multispecific molecule disclosed herein comprises a tumor targeting moiety. In some embodiment, the tumor-targeting moiety comprises an antibody molecule (e.g., Fab or scFv), a receptor molecule (e.g., a receptor, a receptor fragment or functional variant thereof), or a ligand molecule (e.g., a ligand, a ligand fragment or functional variant thereof), or a combination thereof, that binds to a cancer antigen. In some embodiments, the tumor-targeting moiety binds to a cancer antigen present on a cancer, e.g., a hematological cancer, a solid tumor, a metastatic cancer, soft tissue tumor, metastatic lesion, or a combination thereof. In some embodiments, the tumor-targeting moiety binds to a cancer antigen, e.g., BCMA or FcRH5.

In some embodiments, the tumor-targeting antibody molecule binds to a conformational or a linear epitope on the tumor antigen.

In some embodiments of any of the compositions or methods disclosed herein, the tumor-targeting moiety is an antigen, e.g., a cancer antigen. In some embodiments, the cancer antigen is a tumor antigen or stromal antigen, or a hematological antigen.

In some embodiments of any of the compositions or methods disclosed herein, the tumor-targeting moiety binds to a cancer antigen chosen from: BCMA, FcRH5, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD99, CD123, FcRH5, CLEC12, CD179A, SLAMF7, or NY-ESO1, PDL1, CD47, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PMSA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, Gp100/pmel17, Tyrosinase, TRP-1/-2, MC1R, β-catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, MUC-1, CA-125, BAGE, GAGE, NY-ESO-1, 13-catenin, CDK4, CDC27, a actinin-4, TRP1/gp75, TRP2, gp100, Melan-A/MART1, gangliosides, WT1, EphA3, Epidermal growth factor receptor (EGFR), MART-2, MART-1, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RUI1, RUI2, SAGE, TRG, TRP1, TSTA, Folate receptor alpha, L1-CAM, CAIX, gpA33, GD3, GM2, VEGFR, Intergrins (Integrin alphaVbeta3, Integrin alpha5Beta1), Carbohydrates (Le), IGF1R, EPHA3, TRAILR1, TRAILR2, RANKL, (FAP), TGF-beta, hyaluronic acid, collagen, e.g., collagen IV, tenascin C, or tenascin W.

In some embodiments of any of the compositions or methods disclosed herein, the cancer is a solid tumor including but not limited to: pancreatic (e.g., pancreatic adenocarcinoma) cancer, breast cancer, colorectal cancer, lung cancer (e.g., small or non-small cell lung cancer), skin cancer, ovarian cancer, or liver cancer.

In some embodiments of any of the compositions or methods disclosed herein, the cancer antigen or tumor antigen is a hematological antigen. In some embodiments, the cancer or tumor antigen is chosen from one or more of: BCMA, FcRH5, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD99, CD123, FcRH5, CLEC12, CD179A, SLAMF7, or NY-ESO1. In some embodiments, the tumor-targeting moiety binds to one or both of BCMA or FcRH5.

In some embodiments, the tumor-targeting moiety binds to BCMA. In embodiments, the tumor-targeting moiety comprises a BCMA targeting moiety. In some embodiments, the tumor-targeting moiety comprising a BCMA targeting moiety binds to a BCMA antigen on the surface of a cell, e.g., a cancer or hematopoietic cell. The BCMA antigen can be present on a primary tumor cell, or a metastatic lesion thereof. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma. For example, the BCMA antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium. In some embodiments, the tumor targeting moiety comprising a BCMA targeting moiety comprises an anti-BCMA antibody or antigen-binding fragment thereof described in U.S. Pat. Nos. 8,920,776, 9,243,058, 9,340,621, 8,846,042,

7,083,785, 9,545,086, 7,276,241, 9,034,324, 7,799,902, 9,387,237, 8,821,883, US861745, US20130273055, US20160176973, US20150368351, US20150376287, US20170022284, US20160015749, US20140242077, US20170037128, US20170051068, US20160368988, US20160311915, US20160131654, US20120213768, US20110177093, US20160297885, EP3137500, EP2699259, EP2982694, EP3029068, EP3023437, WO2016090327, WO2017021450, WO2016110584, WO2016118641, WO2016168149, the entire contents of which are incorporated herein by reference.

In some embodiments, the BCMA-targeting moiety includes an antibody molecule (e.g., Fab or scFv) that binds to BCMA. In some embodiments, the antibody molecule to BCMA comprises one, two, or three CDRs from any of the heavy chain variable domain sequences of Table 14, or a closely related CDR, e.g., CDRs which have at least one amino acid alteration, but not more than two, three or four alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions) from any of the CDR sequences of Table 14. In some embodiments, the antibody molecule to BCMA comprises a heavy chain variable domain sequence chosen from any of the amino acid sequences of Table 14, or an amino acid sequence substantially identical thereto (e.g., 95% to 99.9% identical thereto, or having at least one amino acid alteration, but not more than five, ten or fifteen alterations (e.g., substitutions, deletions, or insertions, e.g., conservative substitutions)).

In some embodiments, the tumor-targeting moiety binds to FcRH5. In embodiments, the tumor-targeting moiety comprises a FcRH5 targeting moiety. In some embodiments, the tumor-targeting moiety comprising a FcRH5 targeting moiety binds to a FcRH5 antigen on the surface of a cell, e.g., a cancer or hematopoietic cell. The FcRH5 antigen can be present on a primary tumor cell, or a metastatic lesion thereof. In some embodiments, the cancer is a hematological cancer, e.g., multiple myeloma. For example, the FcRH5 antigen can be present on a tumor, e.g., a tumor of a class typified by having one or more of: limited tumor perfusion, compressed blood vessels, or fibrotic tumor interstitium. In some embodiments, the tumor targeting moiety comprising a FcRH5 targeting moiety comprises an anti-FcRH5 antibody or antigen-binding fragment thereof described in U.S. Pat. No. 7,999,077 the entire contents of which are incorporated herein by reference.

In some embodiments of any of the compositions or methods disclosed herein, the cancer is a hematological cancer including, but not limited to: a B-cell or T cell malignancy, e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma (e.g., B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, and acute lymphocytic leukemia. In some embodiments, the hematological cancer is multiple myeloma.

In some embodiments, a multispecific molecule disclosed herein further comprises a cytokine molecule, e.g., one or two cytokine molecules. In some embodiments, the cytokine molecule is chosen from interleukin-2 (IL-2), interleukin-7 (IL-7), interleukin-12 (IL-12), interleukin-15 (IL-15), interleukin-18 (IL-18), interleukin-21 (IL-21), or interferon gamma, or a fragment, variant or combination thereof. In some embodiments, is a monomer or a dimer. In some embodiments, the cytokine molecule further comprises a receptor dimerizing domain, e.g., an IL15Ralpha dimerizing domain. In some embodiments, the cytokine molecule (e.g., IL-15) and the receptor dimerizing domain (e.g., an IL15Ralpha dimerizing domain) are not covalently linked, e.g., are non-covalently associated.

In some embodiments, a multispecific molecule disclosed herein comprises:

(i) an anti-TCRβV antibody molecule (e.g., an anti-TCRβV antibody molecule as described herein); and

(ii) a tumor-targeting antibody molecule (e.g., an antibody molecule that binds to a hematological antigen as described herein, e.g., chosen from one or more of BCMA, FcRH5, CD19, CD22, CD33, CD123, FcRH5, CD179a, or CLEC12).

In some embodiments, the multispecific molecule disclosed herein comprises the anti-TCRβV antibody molecule of (i), the tumor-targeting antibody molecule of (ii) and a cytokine molecule as described herein, e.g., an IL-12 cytokine molecule.

In some embodiments, the multispecific molecule comprises an anti-TCRβV antibody molecule as described herein; and a tumor-targeting antibody molecule that binds to one or both of BCMA or FcRH5. In some embodiments, the multispecific molecule further comprises an IL-12 cytokine molecule. The multispecific molecule can be used to treat a BCMA- or FcRH5-expressing hematological cancer, e.g., multiple myeloma.

In some embodiments, the multispecific molecule comprises an anti-TCRβV antibody molecule as described herein; and a tumor-targeting antibody molecule that binds one or more of CD19, CD22, or CD123. In some embodiments, the multispecific molecule further comprises an IL-12 cytokine molecule. The multispecific molecule can be used to treat a CD19-, CD22-, or CD123-expressing hematological cancer, e.g., leukemia or lymphoma. In some embodiments, the CD19-, CD22-, or CD123-expressing hematological cancer is chosen from a B-cell or T cell malignancy, e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma (e.g., B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, and acute lymphocytic leukemia. In some embodiments, the hematological cancer is multiple myeloma.

In some embodiments, a multispecific molecule disclosed herein further comprises an immunoglobulin constant region (e.g., Fc region) chosen from the heavy chain constant regions of IgG1, IgG2, and IgG4, more particularly, the heavy chain constant region of human IgG1, IgG2 or IgG4. In some embodiments, the immunoglobulin constant region (e.g., an Fc region) is linked, e.g., covalently linked to, one or more of tumor-targeting moiety, the immune cell engager, the cytokine molecule, or the stromal modifying moiety. In some embodiments, an interface of a first and second immunoglobulin chain constant regions (e.g., Fc region) is altered, e.g., mutated, to increase or decrease dimerization, e.g., relative to a non-engineered interface. In some embodiments, the dimerization of the immunoglobulin chain constant region (e.g., Fc region) is enhanced by providing an Fc interface of a first and a second Fc region with one or more of: a paired cavity-protuberance ("knob-in-a hole"), an electrostatic interaction, or a strand-exchange, such that a greater ratio of heteromultimer:homomultimer forms, e.g., relative to a non-engineered interface. In some embodiments,

In some embodiments, a multispecific molecule disclosed herein further comprises a linker, e.g., a linker described herein, optionally wherein the linker is selected from: a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, or a non-helical linker.

In some embodiments, the multispecific molecule comprises at least two non-contiguous polypeptide chains.

In some embodiments, the multispecific molecule comprises the following configuration:

A,B-[dimerization module]-C,-D

wherein:

(1) the dimerization module comprises an immunoglobulin constant domain, e.g., a heavy chain constant domain (e.g., a homodimeric or heterodimeric heavy chain constant region, e.g., an Fc region), or a constant domain of an immunoglobulin variable region (e.g., a Fab region); and

(2) A, B, C, and D are independently absent; (i) an antigen binding domain that preferentially binds to a first immune cell engager comprising an anti-TCRβV antibody molecule disclosed herein; (ii) a tumor targeting moiety (e.g., a tumor-targeting antibody molecule as described herein), (iii) a second immune cell engager chosen from a T cell engager, an NK cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager; (iv) a cytokine molecule; or (v) a stromal modifying moiety, provided that:

at least one, two, or three of A, B, C, and D comprises an antigen binding domain that preferentially binds to a TCRβV region disclosed herein, and

any of the remaining A, B, C, and D is absent or comprises one of a tumor targeting moiety, a second immune cell engager, a cytokine molecule, or a stromal modifying moiety.

In some embodiments, the dimerization module comprises one or more immunoglobulin chain constant regions (e.g., Fc regions) comprising one or more of: a paired cavity-protuberance ("knob-in-a hole"), an electrostatic interaction, or a strand-exchange. In some embodiments, the one or more immunoglobulin chain constant regions (e.g., Fc regions) comprise an amino acid substitution at a position chosen from one or more of 347, 349, 350, 351, 366, 368, 370, 392, 394, 395, 397, 398, 399, 405, 407, or 409, e.g., of the Fc region of human IgG1. In some embodiments, the one or more immunoglobulin chain constant regions (e.g., Fc regions) comprise an amino acid substitution chosen from: T366S, L368A, or Y407V (e.g., corresponding to a cavity or hole), or T366W (e.g., corresponding to a protuberance or knob), or a combination thereof.

In some embodiments, the multispecific molecule further comprises a linker, e.g., a linker between one or more of: the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein and the tumor targeting moiety; the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein and the second immune cell engager, the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein and the cytokine molecule, the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein and the stromal modifying moiety, the second immune cell engager and the cytokine molecule, the second immune cell engager and the stromal modifying moiety, the cytokine molecule and the stromal modifying moiety, the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein and the dimerization module, the second immune cell engager and the dimerization module, the cytokine molecule and the dimerization module, the stromal modifying moiety and the dimerization module, the tumor targeting moiety and the dimerization module, the tumor targeting moiety and the cytokine molecule, the tumor targeting moiety and the second immune cell engager, or the tumor targeting moiety and the antigen binding domain of an anti-TCRβV antibody molecule disclosed herein. In some embodiments, the linker is chosen from: a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, or a non-helical linker. In some embodiments, the linker is a peptide linker. In some embodiments, the peptide linker comprises Gly and Ser. In some embodiments, the peptide linker comprises an amino acid sequence chosen from SEQ ID NOs: 142-145 or 175-178.

In some embodiments of a method or composition for use disclosed herein, the disease is a cancer chosen from: a hematological cancer, a solid tumor, a metastatic cancer, soft tissue tumor, metastatic lesion, or a combination thereof.

In some embodiments of a method or composition for use disclosed herein, the cancer is a solid tumor chosen from: a melanoma, a pancreatic cancer (e.g., pancreatic adenocarcinoma), a breast cancer, a colorectal cancer (CRC), a lung cancer (e.g., small or non-small cell lung cancer), a skin cancer, an ovarian cancer, or a liver cancer. In some embodiments, the cancer is melanoma or CRC.

In some embodiments of a method or composition for use disclosed herein the cancer is a hematological cancer chosen from: a B-cell or T cell malignancy, e.g., Hodgkin's lymphoma, Non-Hodgkin's lymphoma (e.g., B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia), acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, or acute lymphocytic leukemia. In some embodiments, the hematological cancer is multiple myeloma. In some embodiments, the hematological cancer is CLL or DLBCL.

In some embodiments of a method or composition for use disclosed herein the sample from the subject comprises a blood sample, e.g., a peripheral blood sample, a biopsy, e.g., a tumor biopsy, or a bone marrow sample. IN some embodiments, the sample comprises a biological sample comprising immune effector cells, e.g., T cells, or NK cells. In some embodiments, T cells comprise a CD4 T cell, a CD8 T cell, (e.g., an effector T cell or a memory T cell (e.g., a memory effector T cell (e.g., T_{EM} cell, e.g., T_{EMRA} cell), or a tumor infiltrating lymphocyte (TIL).

SEQUENCE LISTING

The patent contains a lengthy sequence listing. A copy of the sequence listing is available in electronic form from the USPTO web site (https://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US12286477B2). An electronic copy of the sequence listing will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

What is claimed is:

1. A method of treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition comprising a multispecific molecule,

wherein the multispecific molecule comprises a first domain that binds to a first target molecule and a second domain that binds to a second target molecule;

wherein the multispecific molecule is a T cell receptor (TCR) agonist;

wherein the second domain comprises a cytokine molecule;

wherein the first domain binds to a T cell receptor beta variable region (TCRβV) of a TCRβ chain expressed by a T cell of the subject;

wherein the TCRβV is TCRβV6, and the first domain comprises a heavy chain variable region (VH) comprising a heavy chain complementarity determining region 1 (HC CDR1), a heavy chain complementarity determining region 2 (HC CDR2), and a heavy chain complementarity determining region 3 (HC CDR3), and a light chain variable region (VL) comprising a light chain complementarity determining region 1 (LC CDR1), a light chain complementarity determining region 2 (LC CDR2), and a light chain complementarity determining region 3 (LC CDR3), wherein:

(a) the HC CDR1, the HC CDR2, the HC CDR3, the LC CDR1, the LC CDR2, and the LC CDR3 comprise the sequences of:

(i) SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 51, SEQ ID NO: 52, and SEQ ID NO: 53, respectively;

(ii) SEQ ID NO:48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56, respectively; or

(iii) SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively;

(b) the HC CDR1, the HC CDR2, and the HC CDR3; and the LC CDR1, the LC CDR2, and the LC CDR3 comprise the HC CDR1 sequence, the HC CDR2 sequence, and the HC CDR3 sequence; and the LC CDR1 sequence, the LC CDR2 sequence, and the LC CDR3 sequence of:

(i) SEQ ID NO: 82 and SEQ ID NO: 81, respectively;

(ii) SEQ ID NO: 85 and SEQ ID NO: 84, respectively;

(iii) SEQ ID NO: 88 and SEQ ID NO: 87, respectively;

(iv) SEQ ID NO: 91 and SEQ ID NO: 90, respectively;

(v) SEQ ID NO: 94 and SEQ ID NO: 93, respectively;

(vi) SEQ ID NO: 97 and SEQ ID NO: 96, respectively;

(vii) SEQ ID NO: 100 and SEQ ID NO: 99, respectively;

(viii) SEQ ID NO: 103 and SEQ ID NO: 102, respectively;

(ix) SEQ ID NO: 106 and SEQ ID NO: 105, respectively;

(x) SEQ ID NO: 109 and SEQ ID NO: 108, respectively;

(xi) SEQ ID NO: 112 and SEQ ID NO: 111, respectively;

(xii) SEQ ID NO: 115 and SEQ ID NO: 114, respectively;

(xiii) SEQ ID NO: 118 and SEQ ID NO: 117, respectively;

(xiv) SEQ ID NO: 121 and SEQ ID NO: 120, respectively;

(xv) SEQ ID NO: 124 and SEQ ID NO: 123, respectively;

(xvi) SEQ ID NO: 127 and SEQ ID NO: 126, respectively;

(xvii) SEQ ID NO: 130 and SEQ ID NO: 129, respectively;

(xviii) SEQ ID NO: 133 and SEQ ID NO: 132, respectively;

(xix) SEQ ID NO: 136 and SEQ ID NO: 135, respectively;

(xx) SEQ ID NO: 139 and SEQ ID NO: 138, respectively;

(xxi) SEQ ID NO: 142 and SEQ ID NO: 141, respectively;

(xxii) SEQ ID NO: 145 and SEQ ID NO: 144, respectively;

(xxiii) SEQ ID NO: 148 and SEQ ID NO: 147, respectively;

(xxiv) SEQ ID NO: 151 and SEQ ID NO: 150, respectively;

(xxv) SEQ ID NO: 155 and SEQ ID NO: 154, respectively;

(xxvi) SEQ ID NO: 158 and SEQ ID NO: 157, respectively;

(xxvii) SEQ ID NO: 161 and SEQ ID NO: 160, respectively;

(xxviii) SEQ ID NO: 164 and SEQ ID NO: 163, respectively;

(xxix) SEQ ID NO: 167 and SEQ ID NO: 166, respectively;

(xxx) SEQ ID NO: 170 and SEQ ID NO: 169, respectively;

(xxxi) SEQ ID NO: 173 and SEQ ID NO: 172, respectively;
(xxxii) SEQ ID NO: 176 and SEQ ID NO: 175, respectively;
(xxxiii) SEQ ID NO: 179 and SEQ ID NO: 178, respectively;
(xxxiv) SEQ ID NO: 182 and SEQ ID NO: 181, respectively;
(xxxv) SEQ ID NO: 185 and SEQ ID NO: 184, respectively;
(xxxvi) SEQ ID NO: 188 and SEQ ID NO: 187, respectively;
(xxxvii) SEQ ID NO: 191 and SEQ ID NO: 190, respectively;
(xxxviii) SEQ ID NO: 194 and SEQ ID NO: 193, respectively;
(xxxix) SEQ ID NO: 197 and SEQ ID NO: 196, respectively;
(xl) SEQ ID NO: 200 and SEQ ID NO: 199, respectively;
(xli) SEQ ID NO: 203 and SEQ ID NO: 202, respectively; or
(xlii) SEQ ID NO: 205 and SEQ ID NO: 204, respectively,

wherein the HC CDR 1 sequence, the HC CDR2 sequence, the HC CDR3 sequence, the LC CDR1 sequence, the LC CDR2 sequence, and the LC CDR3 sequence are determined by the Kabat numbering scheme, the Chothia numbering scheme, or ImMunoGeneTics (IMGT); or

(c) the HC CDR1, the HC CDR2, and the HC CDR3 comprises the HC CDR1 sequence, the HC CDR2 sequence, and the HC CDR3 sequence of SEQ ID NO: 207, SEQ ID NO: 209, SEQ ID NO: 211, SEQ ID NO: 213, SEQ ID NO: 215, SEQ ID NO: 217, SEQ ID NO: 219, SEQ ID NO: 221, SEQ ID NO: 223, or SEQ ID NO: 225; and the LC CDR1, the LC CDR2, and the LC CDR3 comprise the sequences of SEQ ID NO: 51, SEQ ID NO: 52, and SEQ ID NO: 53, respectively, the sequences of SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56, respectively, or the sequences of SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively,

wherein the HC CDR1 sequence, the HC CDR2 sequence, and the HC CDR3 sequence are determined by the Kabat numbering scheme, the Chothia numbering scheme, or ImMunoGeneTics (IMGT);

wherein the first domain comprises a full antibody or an antigen binding domain, wherein the antigen binding domain is selected from the group consisting of a Fab, a $F(ab')_2$, and a single chain Fv (scFv);

wherein the first domain does not bind to any complementarity determining regions of the TCRβ chain and does not bind to an interface of complex of the TCRβ chain and a TCRα chain; and

wherein the multispecific molecule is not immobilized to a solid-phase.

2. The method of claim **1**, wherein the method selectively expands T cells of the subject that express the TCR comprising the TCRβV.

3. The method of claim **1**, wherein

the VH and the VL comprise a sequence having at least 90% sequence identity to the sequence of:

(i) SEQ ID NO: 1 and SEQ ID NO: 2, respectively;
(ii) SEQ ID NO: 9 and SEQ ID NO: 10, respectively;
(iii) SEQ ID NO: 9 and SEQ ID NO: 11, respectively;
(iv) SEQ ID NO: 82 and SEQ ID NO: 81, respectively;
(v) SEQ ID NO: 85 and SEQ ID NO: 84, respectively;
(vi) SEQ ID NO: 88 and SEQ ID NO: 87, respectively;
(vii) SEQ ID NO: 91 and SEQ ID NO: 90, respectively;
(viii) SEQ ID NO: 94 and SEQ ID NO: 93, respectively;
(ix) SEQ ID NO: 97 and SEQ ID NO: 96, respectively;
(x) SEQ ID NO: 100 and SEQ ID NO: 99, respectively;
(xi) SEQ ID NO: 103 and SEQ ID NO: 102, respectively;
(xii) SEQ ID NO: 106 and SEQ ID NO: 105, respectively;
(xiii) SEQ ID NO: 109 and SEQ ID NO: 108, respectively;
(xiv) SEQ ID NO: 112 and SEQ ID NO: 111, respectively;
(xv) SEQ ID NO: 115 and SEQ ID NO: 114, respectively;
(xvi) SEQ ID NO: 118 and SEQ ID NO: 117, respectively;
(xvii) SEQ ID NO: 121 and SEQ ID NO: 120, respectively;
(xviii) SEQ ID NO: 124 and SEQ ID NO: 123, respectively;
(xix) SEQ ID NO: 127 and SEQ ID NO: 126, respectively;
(xx) SEQ ID NO: 130 and SEQ ID NO: 129, respectively;
(xxi) SEQ ID NO: 133 and SEQ ID NO: 132, respectively;
(xxii) SEQ ID NO: 136 and SEQ ID NO: 135, respectively;
(xxiii) SEQ ID NO: 139 and SEQ ID NO: 138, respectively;
(xxiv) SEQ ID NO: 142 and SEQ ID NO: 141, respectively;
(xxv) SEQ ID NO: 145 and SEQ ID NO: 144, respectively;
(xxvi) SEQ ID NO: 148 and SEQ ID NO: 147, respectively;
(xxvii) SEQ ID NO: 151 and SEQ ID NO: 150, respectively;
(xxviii) SEQ ID NO: 155 and SEQ ID NO: 154, respectively;
(xxix) SEQ ID NO: 158 and SEQ ID NO: 157, respectively;
(xxx) SEQ ID NO: 161 and SEQ ID NO: 160, respectively;
(xxxi) SEQ ID NO: 164 and SEQ ID NO: 163, respectively;
(xxxii) SEQ ID NO: 167 and SEQ ID NO: 166, respectively;
(xxxiii) SEQ ID NO: 170 and SEQ ID NO: 169, respectively;
(xxxiv) SEQ ID NO: 173 and SEQ ID NO: 172, respectively;
(xxxv) SEQ ID NO: 176 and SEQ ID NO: 175, respectively;
(xxxvi) SEQ ID NO: 179 and SEQ ID NO: 178, respectively;
(xxxvii) SEQ ID NO: 182 and SEQ ID NO: 181, respectively;
(xxxviii) SEQ ID NO: 185 and SEQ ID NO: 184, respectively;
(xxxix) SEQ ID NO: 188 and SEQ ID NO: 187, respectively;

(xl) SEQ ID NO: 191 and SEQ ID NO: 190, respectively;

(xli) SEQ ID NO: 194 and SEQ ID NO: 193, respectively;

(xlii) SEQ ID NO: 197 and SEQ ID NO: 196, respectively;

(xliii) SEQ ID NO: 200 and SEQ ID NO: 199, respectively;

(xliv) SEQ ID NO: 203 and SEQ ID NO: 202, respectively;

(xlv) SEQ ID NO: 205 and amino acids 140-246 of SEQ ID NO: 204, respectively;

(xlvi) SEQ ID NO: 207 and SEQ ID NO: 10, respectively;

(xlvii) SEQ ID NO: 209 and SEQ ID NO: 10, respectively;

(xlviii) SEQ ID NO: 211 and SEQ ID NO: 10, respectively;

(xlix) SEQ ID NO: 213 and SEQ ID NO: 10, respectively;

(l) SEQ ID NO: 215 and SEQ ID NO: 10, respectively;

(li) SEQ ID NO: 217 and SEQ ID NO: 10, respectively;

(lii) SEQ ID NO: 219 and SEQ ID NO: 10, respectively;

(lii) SEQ ID NO: 221 and SEQ ID NO: 10, respectively;

(liv) SEQ ID NO: 223 and SEQ ID NO: 10, respectively; or

(lv) SEQ ID NO: 225 and SEQ ID NO: 10, respectively.

4. The method of claim **1**, wherein the multispecific molecule comprises at least two non-contiguous polypeptide chains,

wherein a first polypeptide chain of the at least two non-contiguous polypeptide chains comprises a first member of a dimerization module, and a second polypeptide chain of the at least two non-contiguous polypeptide chains comprises a second member of the dimerization module, and

wherein the first polypeptide chain and the second polypeptide chain form a complex via the first member of the dimerization module and the second member of the dimerization module.

5. The method of claim **4**, wherein the first polypeptide chain comprises the first domain and the second polypeptide chain comprises the second domain, and wherein:

(i) the first polypeptide chain comprises the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises the second domain linked to the second member of the dimerization module;

(ii) the first polypeptide chain comprises a first portion of the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises a first portion of the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the first domain and a fourth polypeptide chain comprising a second portion of the second domain;

(iii) the first polypeptide chain comprises a first portion of the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the first domain; or

(iv) the first polypeptide chain comprises the first domain linked to the first member of the dimerization module, and the second polypeptide chain comprises a first portion of the second domain linked to the second member of the dimerization module; wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the second domain.

6. The method of claim **5**, wherein the multispecific molecule further comprises a linker between the first domain and the first member of the dimerization module, a linker between the second domain and the second member of the dimerization module, a linker between the first portion of the first domain and the first member of the dimerization module, a linker between the first portion of the second domain and the second member of the dimerization module, or any combination thereof, and wherein the linker is selected from an IgG hinge, a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non-helical linker.

7. The method of claim **4**, wherein the first polypeptide chain comprises (a) the first domain or a first portion of the first domain and (b) the second domain or a first portion of the second domain, and wherein the first polypeptide chain comprises:

(i) the first domain linked to the first member of the dimerization module linked to the second domain;

(ii) the first portion of the first domain linked to the first member of the dimerization module linked to the first portion of the second domain, wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the first domain and a fourth polypeptide chain comprising a second portion of the second domain;

(iii) the first portion of the first domain linked to the first member of the dimerization module linked to the second domain, wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the first domain; or

(iv) the first domain linked to the first member of the dimerization module linked to the first portion of the second domain, wherein the at least two non-contiguous polypeptide chains comprise a third polypeptide chain comprising a second portion of the second domain.

8. The method of claim **7**, wherein the multispecific molecule further comprises a linker between the first domain and the first member of the dimerization module, a linker between the first portion of the first domain and the first member of the dimerization module, a linker between the first member of the dimerization module and the second domain, a linker between the first member of the dimerization module and the first portion of the second domain, or any combination thereof, and wherein the linker is selected from an IgG hinge, a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non-helical linker.

9. The method of claim **1**, wherein the multispecific molecule comprises a polypeptide sequence comprising:

(i) the first domain linked to the second domain;

(ii) a first portion of the first domain linked to a first portion of the second domain, wherein the polypeptide

sequence further comprises a second portion of the first domain and a second portion of the second domain;

(iii) a first portion of the first domain linked to the second domain, wherein the polypeptide sequence further comprises a second portion of the first domain; or

(iv) the first domain linked to a first portion of the second domain, wherein the polypeptide sequence further comprises a second portion of the second domain.

10. The method of claim **9**, wherein the polypeptide sequence further comprises a linker between the first domain and the second domain, a linker between the first portion of the first domain and the first portion of the second domain, a linker between the first portion of the first domain and the second domain, a linker between the first domain and the first portion of the second domain, or any combination thereof, and wherein the linker is selected from a cleavable linker, a non-cleavable linker, a peptide linker, a flexible linker, a rigid linker, a helical linker, and a non-helical linker.

11. The method of claim **1**, wherein the multispecific molecule further comprises a third domain that comprises a domain that binds to a tumor antigen selected from the group consisting of BCMA, FcRH5, CD19, CD20, CD22, CD30, CD33, CD38, CD47, CD99, CD123, CLEC12, CD179A, SLAMF7, PDL1, gangloside 2 (GD2), prostate stem cell antigen (PSCA), prostate specific membrane antigen (PSMA), prostate-specific antigen (PSA), carcinoembryonic antigen (CEA), Ron Kinase, c-Met, Immature laminin receptor, TAG-72, BING-4, Calcium-activated chloride channel 2, Cyclin-B1, 9D7, Ep-CAM, EphA3, Her2/neu, Telomerase, SAP-1, Survivin, NY-ESO-1/LAGE-1, PRAME, SSX-2, Melan-A/MART-1, gp100/pmel17, Tyrosinase, MC1R, b-catenin, BRCA1/2, CDK4, CML66, Fibronectin, p53, Ras, TGF-B receptor, AFP, ETA, MAGE, CA-125, BAGE, GAGE, CDC27, a actinin-4, TRP1/gp75, TRP2, gangliosides, WT1, Epidermal growth factor receptor (EGFR), MART-2, MUC1, MUC2, MUM1, MUM2, MUM3, NA88-1, NPM, OA1, OGT, RCC, RU11, RU12, SAGE, TRG, TSTA, Folate receptor alpha, L1-CAM, CAIX, gpA33, GD3, GM2, VEGFR, integrin, a carbohydrate, IGFIR, TRAILR1, TRAILR2, RANKL, FAP, TGF-beta, hyaluronic acid, collagen, tenascin C, and tenascin W.

12. The method of claim **1**, wherein the multispecific molecule further comprises a third domain that comprises an NK cell engager, a T cell engager, a B cell engager, a dendritic cell engager, or a macrophage cell engager.

13. The method of claim **12**, wherein the third domain comprises a T cell engager that binds to a TCRβV other than the TCRβV to which the first domain binds.

14. The method of claim **12**, wherein the third domain comprises a T cell engager that does not bind to a TCRβV.

15. The method of claim **1**, wherein the multispecific molecule further comprises a third domain that comprises a domain that binds to CD19 or CD123, or a third domain that comprises a T cell engager that binds to CD3.

16. The method of claim **1**, wherein the multispecific molecule further comprises a third domain that comprises a tumor-targeting domain that binds to a cancer antigen.

17. The method of claim **1**, wherein the multispecific molecule comprises a mutation that decreases Fc receptor binding to the multispecific molecule relative to a multispecific molecule without the mutation.

18. The method of claim **17**, wherein the multispecific molecule comprises a sequence with at least 95% sequence identity to SEQ ID NO: 42.

19. The method of claim **17**, wherein the mutation that decreases Fc receptor binding is an N297A mutation according to EU Numbering in a constant region or corresponds to the alanine at amino acid 180 of SEQ ID NO: 42.

20. The method of claim **1**, wherein the cancer is a hematological cancer, a solid tumor, or a metastatic cancer.

21. The method of claim **20**, wherein the cancer is:

(i) the solid tumor, wherein the solid tumor is pancreatic cancer, breast cancer, colorectal cancer, lung cancer, skin cancer, ovarian cancer, or liver cancer; or

(ii) the hematological cancer, wherein the hematological cancer is a B-cell malignancy or a T cell malignancy.

22. The method of claim **21**, wherein the cancer is the hematological cancer, and the B-cell malignancy or the T cell malignancy is Hodgkin's lymphoma, Non-Hodgkin's lymphoma, acute myeloid leukemia (AML), chronic myeloid leukemia, myelodysplastic syndrome, multiple myeloma, or acute lymphocytic leukemia.

23. The method of claim **22**, wherein the cancer is the hematological cancer, and the B-cell malignancy is Non-Hodgkin's lymphoma, and wherein the Non-Hodgkin's lymphoma is B cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, or hairy cell leukemia.

24. The method of claim **1**, wherein the cytokine molecule is selected from the group consisting of interleukin-2 (IL-2) or a functional fragment or variant thereof, interleukin-7 (IL-7) or a functional fragment or variant thereof, interleukin-12 (IL-12) or a functional fragment or variant thereof, interleukin-15 (IL-15) or a functional fragment or variant thereof, interleukin-18 (IL-18) or a functional fragment or variant thereof, interleukin-21 (IL-21) or a functional fragment or variant thereof, and interferon gamma or a functional fragment or variant thereof.

25. The method of claim **1**, wherein the cytokine molecule comprises a sequence with at least 95% sequence identity to SEQ ID NO: 2170, SEQ ID NO: 2180, SEQ ID NO: 2191, SEQ ID NO: 2270, SEQ ID NO: 2280, or SEQ ID NO: 2320.

26. The method of claim **1**, wherein the second domain binds to a second target molecule expressed by the same T cell expressing the TCRβV to which the first domain of the multispecific molecule binds.

27. The method of claim **26**, wherein binding of the first domain to the TCRβV and binding of the second domain to the second target molecule promotes the T cell to kill cancer cells.

28. The method of claim **1**, wherein

the VH and the VL comprise the sequence the sequences of:

(i) SEQ ID NO: 1 and SEQ ID NO: 2, respectively;

(ii) SEQ ID NO: 9 and SEQ ID NO: 10; respectively;

(iii) SEQ ID NO: 9 and SEQ ID NO: 11; respectively;

(iv) SEQ ID NO: 82 and SEQ ID NO: 81, respectively;

(v) SEQ ID NO: 85 and SEQ ID NO: 84, respectively;

(vi) SEQ ID NO: 88 and SEQ ID NO: 87, respectively;

(vii) SEQ ID NO: 91 and SEQ ID NO: 90, respectively;

(viii) SEQ ID NO: 94 and SEQ ID NO: 93, respectively;

(ix) SEQ ID NO: 97 and SEQ ID NO: 96, respectively;

(x) SEQ ID NO: 100 and SEQ ID NO: 99, respectively;

(xi) SEQ ID NO: 103 and SEQ ID NO: 102, respectively;

(xii) SEQ ID NO: 106 and SEQ ID NO: 105, respectively;

(xiii) SEQ ID NO: 109 and SEQ ID NO: 108, respectively;

(xiv) SEQ ID NO: 112 and SEQ ID NO: 111, respectively;
(xv) SEQ ID NO: 115 and SEQ ID NO: 114, respectively;
(xvi) SEQ ID NO: 118 and SEQ ID NO: 117, respectively;
(xvii) SEQ ID NO: 121 and SEQ ID NO: 120, respectively;
(xviii) SEQ ID NO: 124 and SEQ ID NO: 123, respectively;
(xix) SEQ ID NO: 127 and SEQ ID NO: 126, respectively;
(xx) SEQ ID NO: 130 and SEQ ID NO: 129, respectively;
(xxi) SEQ ID NO: 133 and SEQ ID NO: 132, respectively;
(xxii) SEQ ID NO: 136 and SEQ ID NO: 135, respectively;
(xxiii) SEQ ID NO: 139 and SEQ ID NO: 138, respectively;
(xxiv) SEQ ID NO: 142 and SEQ ID NO: 141, respectively;
(xxv) SEQ ID NO: 145 and SEQ ID NO: 144, respectively;
(xxvi) SEQ ID NO: 148 and SEQ ID NO: 147, respectively;
(xxvii) SEQ ID NO: 151 and SEQ ID NO: 150, respectively;
(xxviii) SEQ ID NO: 155 and SEQ ID NO: 154, respectively;
(xxix) SEQ ID NO: 158 and SEQ ID NO: 157, respectively;
(xxx) SEQ ID NO: 161 and SEQ ID NO: 160, respectively;
(xxxi) SEQ ID NO: 164 and SEQ ID NO: 163, respectively;
(xxxii) SEQ ID NO: 167 and SEQ ID NO: 166, respectively;
(xxxiii) SEQ ID NO: 170 and SEQ ID NO: 169, respectively;
(xxxiv) SEQ ID NO: 173 and SEQ ID NO: 172, respectively;
(xxxv) SEQ ID NO: 176 and SEQ ID NO: 175, respectively;
(xxxvi) SEQ ID NO: 179 and SEQ ID NO: 178, respectively;
(xxxvii) SEQ ID NO: 182 and SEQ ID NO: 181, respectively;
(xxxviii) SEQ ID NO: 185 and SEQ ID NO: 184, respectively;
(xxxix) SEQ ID NO: 188 and SEQ ID NO: 187, respectively;
(xl) SEQ ID NO: 191 and SEQ ID NO: 190, respectively;
(xli) SEQ ID NO: 194 and SEQ ID NO: 193, respectively;
(xlii) SEQ ID NO: 197 and SEQ ID NO: 196, respectively;
(xliii) SEQ ID NO: 200 and SEQ ID NO: 199, respectively;
(xliv) SEQ ID NO: 203 and SEQ ID NO: 202, respectively;
(xlv) SEQ ID NO: 205 and amino acids 140-246 of SEQ ID NO: 204, respectively;
(xlvi) SEQ ID NO: 207 and SEQ ID NO: 10, respectively;
(xlvii) SEQ ID NO: 209 and SEQ ID NO: 10, respectively;
(xlviii) SEQ ID NO: 211 and SEQ ID NO: 10, respectively;
(xlix) SEQ ID NO: 213 and SEQ ID NO: 10, respectively;
(l) SEQ ID NO: 215 and SEQ ID NO: 10, respectively;
(li) SEQ ID NO: 217 and SEQ ID NO: 10, respectively;
(lii) SEQ ID NO: 219 and SEQ ID NO: 10, respectively;
(lii) SEQ ID NO: 221 and SEQ ID NO: 10, respectively;
(liv) SEQ ID NO: 223 and SEQ ID NO: 10, respectively; or
(lv) SEQ ID NO: 225 and SEQ ID NO: 10, respectively.

29. The method of claim **1**, wherein the first domain comprises a sequence having at least 90% sequence identity to any one sequence selected from the group consisting of SEQ ID NOs: 80, 83, 86, 89, 92, 95, 98, 101, 104, 107, 110, 113, 116, 119, 122, 125, 128, 131, 134, 137, 140, 143, 146, 149, 153, 156, 159, 162, 165, 168, 171, 174, 177, 180, 183, 186, 189, 192, 195, 198, 201, 204, 206, 208, 210, 212, 214, 216, 218, 220, 222, and 224.

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